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PREFACE

The Editors are conscious of the suggestions made by a number of helpful readers and reviewers. Two suggestions in particular we are trying to heed. The first is that the selection of authors be more international. The second is that with the greater complexity of each general area an intense consideration of a portion is superior to a skimming over of the whole While we preserve general headings, such as Infectious Diseases or Cardiovascular Diseases, for the sake of orientation and continuity and to indicate a framework to be rounded out periodically, we urge the authors to something less than complete coverage. We prefer a thoughtful presentation, suitably subtitled, of that part of the field in which the author is most at home, plus a few concise paragraphs in which he reflects on other portions of the field. Every reader likes the latter to compare his interpretations with those of the "expert."

It will be noted that the five year terms of service of each member of the editorial board now begin to introduce new names to the board. The new thank the old for their conscientious and selfless pioneering.

Once again, we are most grateful for the assiduousness of the members of the Review office, in particular Mrs Carol Kupke, Miss Jean Kaye, and Miss Bea Morrow.

J S.L B E M MACK.
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TOPICS AND AUTHORS
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CONTENTS

INFECTIOUS DISEASES[1]

By William S. Tillett

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The magnitude and universality of the clinical usages of antibiotic reagents has now reached such proportions that they dominate all forms of therapy. As an example, in one large metropolitan hospital over half of an annual budget of $700,000 is spent for drugs. From an analysis of the total subject of microbial antibiosis, recent investigations indicate that new phases of special interest and probable importance are developing. They represent shifts in emphasis from the first phase.

Beginning with the first effective treatment of patients with bacteriostatic and bactericidal reagents, the first phase has been characterized by the eager search for new material that would prove serviceable in the treatment of the infections caused by bacterial species against which each preceding one has not been entirely satisfactory. This type of exploration is still in progress, including agents that might prove antiviral. The problem of the first phase is a well defined one. Its prime emphasis is on the antimicrobial qualities of the reagents, first observed *in vitro*, and then tested *in vivo*, in experimentally infected animals, and finally administered to patients.

The second phase, discussions of which will constitute the body of this report, deals with some of the complexities of the situation which are beginning to emerge in a previously unpredicated fashion. At first, being looked upon as collateral findings secondary to curing patients with primary infectious diseases, they now are assuming special importance in their own right. Although they represent early studies in topics that invite further elaboration, it is not premature to attempt to bring out by discussion not only the results themselves but also, and perhaps of greater importance, the fact that they are illustrative of future trends and problems to be anticipated in an Antibiotic World.

Before proceeding with a consideration of the particular studies to be reviewed in this article it is not inappropriate to attempt to portray the scope and magnitude of The Antibiotic Era as it has gained momentum since first sulfanilamide and then penicillin have revolutionized not only the mortality and morbidity of infectious diseases but have also redirected the thinking in the fields of research and clinical study that pertain to infective agents and the diseases that they produce.

The magnitude of the clinical usages of antibiotics warrants clear visualization. It is estimated that during the peak winter months the production of the most widely used antibiotics of fungal origin amounts to 70 tons per month, 20 tons of which are penicillin In addition, even though the fungal

[1] The survey of literature pertaining to this review was completed in September, 1952.

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each place in the economy of nature, if any one species does not become modified *and improved in a corresponding degree with its competitors, it will be exterminated.* Unless favourable variations be inherited by some at least of the offspring nothing can be effected by natural selection.

Observations on the bacterial population of man, pathogenic and nonpathogenic, have offered, and continue to offer, an unusual opportune method of noting changes induced by antibiotic effects. One of the manifestations is the alterations in the number and species of microorganisms which constitute the so-called normal flora of sites of the body which have contact with the exterior and whose surfaces, therefore, are normally contaminated Reorientations of these bacterial populations, as so far noted, have usually been temporary for the duration of therapy, after which reversion to the previous state has occurred but not necessarily completely. It requires no more than a moderate imaginative effort to envisage a not too distant future period when the florae of the expósed areas of this body which have been created and presided over by universal "antibioticism" will become the so-called normal flora. The data derived from clinical bacteriology *will contribute to a set of future normal standards for man essentially* different from those of the past.

The change in the bacterial flora need not be viewed with undue concern It is not a great price to pay, on the one hand, for the profound decrease in the mortality of essentially all of the severe acute bacterial diseases that have been identified since the beginning of bacteriology, and, on the other hand, for the effective or potentially effective prevention of many of them This has been indicated by their practical effectiveness in meningococcus meningitis, venereal diseases, and a reduction in the incidence of their sequelae including syphilis of the central nervous system and cardiovascular system, septic sore throat, and rheumatic fever, with, in addition, the further extension of antibiotic prophylaxis utilizing the reagents now at hand or yet to come. On the basis of the generalities just given, the articles which will be reviewed concerning alterations in bacterial flora with or without subsequent untoward complications, as well as the other selected topics, will be commented upon not only from the standpoint of practical clinical features, but also as significant contributions to identifying the early emergence *of what may prove to be significant biological evolution,* primarily affecting the bacterial species themselves and secondarily in contributing to an understanding of the significance of microorganisms, as they exist in and on man, as useful or harmful adjuvants

Attention may be directed first to observations that have been made on alterations in bacterial populations of various anatomical sites, notably the throat, which have occurred in absence of local abnormalities In addition, special interest has centered around the bacteriological findings noted in association with local pathological changes occurring during the period of antibacterial medication and not related directly to the primary disease for which the specific treatment was first instituted.

antibiotics have replaced the sulfonamide drugs in the treatment of many diseases, the amounts of the latter that are administered to patients continue to be of enormous proportions.

Applying some not too technical figuring it may be deduced that 70 tons of antibiotics per month amount to 63,500,000 gm. per month. Estimating a gram as a daily dose and including other less widely used preparations, and adding the sulfonamides, it is not seriously incorrect to estimate that up to 1,000,000,000 doses are distributed among the population of 150,000,000 people of this country per year. There is no evidence to indicate that a decrease in the treatments will occur in the near future unless prevention of the infections, for which the therapy is so effective, substantially decreases their incidence. Furthermore, if, as and when antibiotics effective against viral infections become available, additional substantial increases may be *reasonably expected.*

To indicate the extent of the expansion of antibiosis, one may also include the development of antibiotic administration to animals for nutritional effects (1, 19, 20, 21) other than the treatment of specific diseases And finally, notation may be made of their use in hastening the maturation of seeds and the growth of seedlings (2). It is clear, therefore, that the administration of antibiotic reagents is a permanent aspect of human living of profound proportions affecting it both directly and indirectly, and is here to stay during the forseeable future. There is scarcely an individual in this country who has not received antibiotic therapy on some occasion or other, or even many times, and who will not receive them many times more in the future. In addition, it seems essentially inevitable that in a substantial part of the biological world, significant changes may be expected, and, as will be subsequently indicated, are even now in evidence in certain fields In its broadest sense, the phenomena constitute an example of a stage of biological evolution being observed, as it occurs in its incipiency.

Viewed from the point of view of the members of the microbiological races, *many bacterial species, notably the so-called pathogenic ones, are* faced with the serious threat of extinction To meet this challenge, certain basic principles of evolution have come into play Through the survival of the fittest, strains with specifically acquired antibiotic resistance have come into existence and bacterial species with natural resistance have become more conspicuous Even more unique, other strains of pathogens, as demonstrated by Miller & Bohnhoff (3), have emerged that are dependent on the presence of certain antibiotics in their culture medium for the maintenance of their viability and multiplication, otherwise they perish

It is of interest, therefore, in considering the evolutionary changes among microorganisms that have been set in motion by their increasing contact with antibiotics to recall that Darwin in "The Origin of the Species" has expressed this principle as follows

Though nature grants long periods of time for the work of natural selection, she does not grant an indefinite period, for as all organic beings are striving to seize on

antibiotic resistance. Thirdly, "new" species of antibiotic-unsusceptibles become implanted and may increase in population so that they dominate the total flora.

However, there have not yet been sufficiently extensive and comprehensive total bacteriological surveys of all body areas simultaneously performed, with normal conditions existing both before and during antibiotic administration, to be able to construct a complete picture of the mass changes that may occur without the implications of disease. Furthermore, the changes in each of the individual body sites mentioned above have not yet been as well studied as the oral-pharyngeal area. Studies of the above types are also limited by the fact that the rate of and completeness of the return to the previous flora after cessation of the drugs is not yet sufficiently well established on an extensive scale to be able to draw final conclusions. It appears, at present however, that there is a tendency to return to the pretreatment species of organisms.

The situation in so far as it is known, presents some interesting problems which warrant discussion. For example, when coliform organisms became temporarily established in the throat, the gram-positive species appeared to be able subsequently to force the colon bacilli out when the antibiotic effect has ceased. *E. coli* is a robust species of microorganism. When mixed in artificial culture media, or when existing in mixed suppurative infections, its capacity for growth and the maintenance of its presence is not impaired by the other organisms, and it often even outgrows them.

Using another species as an example, it appears that yeast cells (*Monilia albicans*) absent from, or present in the normal hygienic mouth in modest numbers, increase during antibiotic administration to a degree to dominate quantitatively the total flora and with cessation of the state of antibiosis the monilia return to the pretreatment level. These circumstances pose the question of why, when *E. coli* or yeast cells were the dominant organisms, they did not maintain this position instead of receding to the previously existing status during the post treatment period? The behavior of many of the other organisms involved in the transformation of the "normal" flora could be subjected to the same questioning The situation has factors in common with the so-called carrier state Individuals who harbor in their throats pathogenic organisms such as diphtheria bacilli, hemolytic streptococci, or meningococci are called carriers The nonpathogenic organisms similarly present are referred to as the normal flora The problem is posed, therefore, of whether or not the antibiotically induced flora is dependent upon conditions comparable to that which accounts for the pathogenic carrier states or to that which is responsible for the normal flora, or to factors peculiar to the state of antibiosis and not related to either carrier state or normal flora. Although the subject cannot be more than mentioned here it should be pointed out that it is not solely an academic one, but has practical clinical aspects to be brought out in the section that follows immediately. In any case, the subject is provocative of thoughtful consideration.

Alterations in Normal Bacterial Flora without Demonstrable Local Diseases

The body sites involved include the oral, nasopharyngeal, respiratory, intestinal and genital, and the skin. Since the chief interest of bacteriological cultural studies has arisen from the complicating local diseases that have occurred during antibiotic therapy, the number of observations on changes in flora without local disease have been limited. Lipman, Coss & Boots (4) in 1946 reported studies of the throat and intestinal flora of patients with rheumatoid arthritis to whom penicillin was given for several months. The pretreatment flora was predominantly gram-positive organisms sensitive to penicillin. During treatment gram-negative organisms, especially *Escherichia coli* predominated Changes in the intestinal flora, notably the disappearance of nonhemolytic streptococci from the stools, also occurred but were less striking than those of the throat. Smith & Bloomfield (5) also noted the appearance of a coliform flora in the throat of normal persons receiving penicillin. These same authors in a study of the newborn found that the administration of penicillin suppressed the appearance of the normal flora of the throat for several days. Miller & Bohnhoff (6) noted an unusually high incidence of yeastlike organisms in the throats of patients undergoing treatment with streptomycin No local symptoms developed

Long (7) noted that during the first few days of treatment with penicillin that *Hemophilus influenzae*, *Neisseria pharyngis sicca*, and *Monilia albicans* were the only organisms demonstrable by culture, the penicillin sensitive species having disappeared During a second phase, while treatment was being continued, bacterial invasion of the oral cavity occurred with members of the *Bacterium* group (aerogenes, coli, and others). Weinstein (8) has particularly noted *H. influenzae*, *K pneumoniae*, and *Staphylococcus aureus*, and in addition *E. coli*, and members of the *Neisseria* group. Subsequent reference will be made to Weinstein's findings with respect to the occurrence of disease resulting from the above organisms

Kligman (9) observed that patients treated with antibiotics had unusually large numbers of *Candida albicans* in their mouths without glossitis or stomatitis.

Metzger *et al* (10) observed that aureomycin altered intestinal flora by reducing the numbers of coliform organisms, yeast, and anaerobes in the stools *Bacillus proteus*, staphylococci and streptococci proliferated in some cases. Brown (11) noted that aureomycin orally administered was followed by increase in *C. albicans* in stools.

The currently accepted basis for the effect of the antibiotics on the oral-nasopharyngeal and intestinal flora is that the antibiotic-sensitive species, chiefly gram-positive cocci, are first destroyed, sometimes yielding sterile cultures for brief periods (5, 7) Next, the antibiotic-unsusceptible species which were present as part of the normal pretreatment flora persists together with organisms which may have originally possessed or have acquired specific

ondarily in areas of dermatitis. He stated further that cutaneous moniliasis had well defined clinical characteristics. Consequently, when monilia have been isolated by culture from cases of cutaneous disease, not clinically identifiable as cutaneous moniliasis, but treated by the topical application of antibiotic ointments their significance, if any, remains obscure.

In extending the subject, Kligman has further cited the unusual difficulty in establishing with certainty the diagnosis of pulmonary moniliasis, chiefly because of the fact that the tissues involved are not accessible for direct inspection particularly in nonfatal cases.

In general clinical practice, pulmonary moniliasis may be suspected in patients who have pneumonitis not of the classical clinical varieties and from whose sputa *C. albicans* may be cultured in large quantities. Kligman calls attention to the fact that this organism not uncommonly establishes itself as a secondary invader of pathological tissues. Consequently in patients with atypical types of pneumonitis the fact that *C. albicans* is present leaves its essential etiological significance in doubt.

As a passing comment in connection with efforts to promote the diagnosis of pulmonary moniliasis, it is important to recognize as a practical point of procedure the necessity of having such a patient cleanse his mouth unusually thoroughly and repeatedly just prior to supplying a specimen of sputum, and of obtaining the specimen in the presence of the examiner to insure its true bronchial origin and so exclude contamination by saliva containing yeast cells. Finally, in emphasizing the difficulties of the diagnostic problem, Kligman points out that the local pathology may primarily be due to other conditions such as vitamin deficiency, allergic reactions, other bacterial and viral infections, or other irritations overlayed with moniliasis.

The antibiotic-vitamin relationship has been receiving attention in recent years. In the clinical field, Ellinger & Shattock (17) cited a case of clinical nicotinamide deficiency associated with local treatment of oral cavity with penicillin In addition black tongue appeared. The symptoms disappeared after discontinuance of the drug and the administration of nicotinic acid. The authors noted the fact that whereas black tongue is a sign of nicotinamide deficiency in dogs it has not previously been described in the same deficiency state in man

Williams (18) has reported that among 200 patients receiving chloramphenicol, 12 developed black tongue and stomatitis as a result of infection with *M. albicans*. It began in the fourth to sixth day of therapy. The majority of the patients were either chronically ill or elderly Supplementary vitamins did not prevent glossitis but black tongue did not occur in three patients treated with vitamins

In animal husbandry, aureomycin has been given to normal young chicks, calves, lambs, etc , and observation made on their increased growth and rate of fattening (19, 20, 21) Linkswiller, Bauman & Snell (22) have described the increased growth of rats which occurred during aureomycin administration, and have suggested that the antibiotic operated by eliminating in-

Alterations in Normal Bacterial Flora with the Subsequent Development of Complicating Diseases

Weinstein (8) who first called attention to the interesting Scylla-Charybdis feature of antibiotic therapy reported a patient with *H. influenzae* meningitis who while being treated with streptomycin developed bronchopneumonia and meningitis due to *Staphylococcus aureus*. The same author subsequently extended the study to include a report of 5 patients who developed as a secondary complication of extensive treatment with penicillin and/or streptomycin bacterial infections with such organisms as *H. influenzae*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* The bacterial species involved in the secondary disease had been observed by throat cultures to increase during the period of antibiotic treatment

Somner & Favour (12) have cited four patients in whom penicillin therapy was followed by complicating pneumonia due to gram negative organisms. The appearance and possible disease-producing significance of fungi in association with antibiotic therapy has received more attention than the bacteria. The isolation of *C. albicans* in large numbers, including pure cultures, has been the subject of many reports. Where active local disease became evident, etiological significance has been given to the presence of the monilia. *Candida albicans* has been the most conspicuous of the yeast cells isolated from all the areas of the body involved; Harris (13) reported finding this species in stools in association with lesions of oral mucous membranes and, in females, in perianal and vulval areas in association with local irritative conditions. Woods and co-workers (14) observed monilia in oropharynx, bronchopulmonary, and intestinal areas in association with diseases which they considered to be moniliasis. In addition to the preponderance of reports which have noted the abundance of *Monilia albicans* in association with oral, respiratory and gastrointestinal and dermatological symptomatology and pathology, other reports (15) have cited generalized moniliasis as the most serious and fatal complication of this category Yow (16) observed proteus and pseudomonas infections complicating treatment with a variety of the more commonly employed antibiotics.

Kligman (9) in a recent article has subjected the problem of moniliasis occurring in connection with antibiotic therapy to detailed and careful scrutiny, and, as a result he has challenged the correctness of the concept of the primary etiological significance of *M. albicans* based on its presence in large quantities as indicated in the previous articles In considering the oral findings, Kligman reported that monilia may be detected in large quantities on the oral surfaces of patients receiving antibiotic therapy but without local disease [see also Miller & Bohnhoff (6)] He also stated that although thrush is a classical disease of monilial etiology, it was uncommon following antibiotic therapy.

In considering the relationship of monilia to cutaneous diseases, Kligman stated that, in contrast to the mouth, *C. albicans* is not part of the normal flora of the skin nor does it have the tendency to become established sec-

when infection is attempted under different conditions. Similarly any definition of resistance or immunity must include a consideration of the microorganism against which the resistance is present or absent; an individual host may be resistant or susceptible to one strain or species or may vary in resistance or susceptibility to the same strain under varying conditions. The above analysis of the special subject of etiology has been detailed because the problems that are involved in the significance of the side effects of antibiotic therapy have become increasingly evident and may be expected to assume greater proportions.

The secondary bacterial and fungal agents, found in association with the diseases that have been noted to occur during antibiosis, are in most instances grouped under species usually considered saprophytes or secondary invaders Consequently, it is useful to consider certain general points which characterize these types of chronic infection with open drainage and exposure as seen without the antibiotic factor. One basis for their existence and occurrence is the damaged state of the underlying tissues The damaging event may have been accidental, or surgical trauma, or disease; under these conditions the otherwise saprophytic organisms are capable of living and multiplying extensively in the coagulums and exudations accumulated at the diseased area and assist in maintaining the pathology previously created by the other circumstances

One method of therapeutic attack upon the types of diseases exhibiting the factors of pathogenesis just outlined, is to rectify the underlying abnormality by abolishing either the hemorrhagic materials, or the exudative materials, or both, that primarily support the growth of the bacteria and by this means bring about sterilization of the area. Examples of this course of events have been observed in patients treated with the streptococcal enzymes, Streptokinase-Streptodornase (Varidase) (24). One illustrative case was as follows: A patient, following pneumonectomy, developed postoperatively collections of blood within the thoracic cage. *Pseudomonas aeruginosa* became implanted in the coagulum. Following an initial liquefaction of the coagulum with Streptokinase-Streptodornase (Varidase) and subsequent effective drainage, *Ps. aerogenes* persisted. Various antibiotics were introduced into the thoracic space without effect. Then Varidase was introduced on each of three alternate days with appropriate aspiration following enzymatic liquefaction. The colony count of *Ps aerogenes* progressively decreased and sterility was obtained on the sixth day from beginning the treatments coincident with the abolition of all the surface deposits This case, as well as others which followed the same course, demonstrated that the presence of the saprophytic secondary invaders in abundance was conditioned by, and dependent upon, the special local tissue pathology, which superseded in importance the pathogenic characteristics of the bacteria and minimized their significance as primary etiological agents of disease From the standpoint of pathogenesis of the preceding types of illnesses, optimal therapy may be directed at correcting the underlying pathology of the

testinal microorganisms that otherwise utilized or destroyed the growth promoting nutrient vitamin B6.

This interesting relationship of antibiotics and nutrition at present offers certain apparent paradoxes that remain to be resolved. On the one hand, in patients, as previously cited, the antibiotic administration has been associated with the development of abnormalities ascribed to states of vitamin deficiency and, on the other hand, the same administration to animals has been followed by increased growth which is ascribed to greater availability of vitamins. One phase of the problem appears to be related to which species of organisms may destroy ingested nutritional material and which species may synthesize nutritional adjuvants. The subject, particularly in man, is a striking illustration of a problem representing the second phase of antibiosis, previously referred to, and awaits further study with predictably interesting disclosures.

In view of the fact that phases of the subject which have been described are assuming increasing importance containing both implications and complications, it is useful to consider the kind of evidence that will justify the conclusion that a particular disease is caused by a particular microbiological parasite. The broad subject of infection and resistance is the classical category for these particular types of problems. From the standpoint of the etiological significance of the bacterium or fungus, it is useful to recall the so-called Koch's postulates. Although it has been stated (23) that there is no clear evidence Koch ever laid them down in the specific details ascribed to them, the individual points are about as follows: (*a*) *The microorganism should be found in the pathological areas of all cases of the disease in question*; (*b*) *The microorganism should be cultured in pure form outside the body*; (*c*) The microorganism should reproduce the disease in susceptible animals; (*d*) The microorganism identical with that first obtained should be isolated from the infected animal

It is now obvious that experience has taught that the requirements of the four points cannot always be fulfilled, nor are they always necessary. There are available additional methods of serology, cutaneous reactions, and others that can supplement other pieces of partial information to contribute to the established final convincing result. Nor is it the purpose of this article to elaborate on this field, but since Koch's postulates served in the beginnings of bacteriology the greatest possible service in promoting correct determinations of true bacterial etiology of specific infectious diseases, their restatement now constitutes a refreshening reminder that the newer problems of etiology, which accompany the second phase of the antibiotic era, also require careful and critical analysis. Returning to a consideration of the factors that constitute infection, it should be recognized that, as a general principle, any definition of bacterial virulence or infectivity must include a consideration of the host; a bacterial species or even individual strains of the same species may be pathogenic for one species of animal and not another, or may not exhibit the same pathogenicity for members of the same species

the usual low virulence of the infecting strains is compensated for by the large quantities present to serve as an inoculum. The normally resistant portal of entry of the host (patient's tissues) being damaged by local disease affords a susceptible site of bacterial invasion, particularly when the usually effective total circulatory immune processes are depressed.

It seems obvious that in order to circumvent these complicating diseases it is not necessarily required to reduce antibiotic therapy which may be so effective in its primary purpose and even save lives, but to broaden the planning of total treatment to take into account the debility, the senile changes, and the low grade tissue damage with or without exudative materials present.

Synergisms and Antagonisms among Antibiotic Reagents

The previous portions of this article have dealt with factors relating to the bacterial species associated with diseases that have become prominent under the special conditions created by antibiosis, and also with conditions of the patient that have assumed importance in the special antibiotically developed parasite-host relationship An additional relatively new and interesting phase of the broad subject centers around the antibiotic reagents themselves as implied in the heading of this section.

With an increasing number of antibacterial reagents becoming available at a relatively rapid rate, their usage at the practical clinical level has been characterized by an increase in the simultaneous administration of two or more. Statements may be read to the effect that there is an increasing number of infections in man that are not cured by a single antibiotic. The presumed increase is in all probability more apparent than real The situation may be more correctly appraised by noting that, since the great majority of the classical primary bacterial infections are now curable rapidly and effectively by any one of several antibiotics, the residuum of unsuccessfully treated infections is now more conspicuous as a continuing problem of therapy. It constitutes a considerable body of a hospital population and accordingly appears to be on the increase although it has always been present to the same degree.

Being faced with the problems of treatment presented by the types of infection, most often subacute or chronic, mentioned above, and having available multiple potentially effective therapeutic reagents, clinical trial has preceded considerably the specific information derived from experimental data pertinent to the subject

The rationale of such clinical procedures has rested either upon the premise that two or three weapons of attack are better than a single one, or, more particularly, that in the conspicuously refractory types of infection just mentioned multiple causative bacteria are involved, some of which may be refractory to one antibiotic and not to another. Consequently, advantage should be taken of the individual specificities of each of several antibacterial drugs operating simultaneously against all the microorganisms of primary

tissues themselves or of eradicating the nutritional and protective factors afforded the microorganisms by the exudations. With either or both of these procedures effectively accomplished, direct attack on the secondarily infecting organims by antibiotic reagents is obviously not the only useful method of treatment. Consequently, successful treatment does not necessarily depend on the finding of a new antibiotic to which the types of organisms mentioned are highly susceptible. The situation as described with saprophytic types of infection, differs sharply from primary infections caused by highly virulent organisms such as pneumococcal lobar pneumonia where the destruction of the invasive bacteria is of paramount importance.

When the secondary types of infection have assumed the characteristics of invasion with septicemia, the factor of massive numbers of organisms accumulated in damaged tissues which serve as an unusually wide open portal of entry contributes to the clinical state. In this total problem of the complicating secondary infections that arise during antibiotic therapy particular importance lies in identifying and rectifying the latent abnormalities which may under conditions of extensive antibiotic medication give rise to the complications that have been discussed.

In reconsidering the cases in which the immediate cure of one bacterial infection has been followed by another infection with an associated bacterial agent, the situation as derived from the reported studies of the subject may be summarized as follows: From the standpoint of the microorganisms: (a) According to species identification, with few exceptions, those described are not regularly classified as primary pathogens; (*b*) They have been, for the most part, present quantitatively in unusually large numbers at the local sites. It also may be noted that in not a few instances they were present in areas of the body where they are not usually found; (*c*) From the standpoint of the host, i.e., patient, it has been noted, and stressed by the authors, that the patients were either debilitated, for in the older age groups or both or had an unrelated low grade disease at the site of the secondary complication. Somner & Favour (12) discuss in particular the poor condition of their patients with low resistance to infection as evidenced by low serum proteins and leukopenia. Two of the patients had complicated surgical conditions without pulmonary disease on which the gram-negative bacillary pneumonias were superimposed; the remaining two patients were complicated medical problems, having previously had varied respiratory illnesses. As previously noted, the vicious cycle of antibiosis inducing or associated with vitamin deficiency, which in turn creates local pathology, which in turn becomes vulnerable to the otherwise noninvading types of microorganisms is important. Finally with respect to the host, pre-existing areas of low grade disease of diverse chronic types have served as the significant defect.

Viewing the situation, therefore, from the standpoint of the basic principles of infectivity and virulence of bacteria, on the one hand, and resistance and susceptibility of the host on the other, it seems reasonable to deduce that in the complicating infections arising in association with antibiotic therapy,

compounds with special properties were being developed, clinical trials were being made of mixtures of the various sulfonamide compounds in order to retain the special advantages of each but obviate the untoward side effects and toxicities of each.

As the antibiotics of fungal origin have increased in number, particularly in view of the simplicity of their administration and the broad spectrum of their actual and potential effects, the refractory types of infections previously referred to have been subjected to vigorous multiple antibiotic treatments. In not a few instances there were strikingly favorable therapeutic effects not otherwise attainable. It remains to define, through quantitative and qualitative experimental procedures, the special conditions through which the total antibiotic therapy may be further enhanced.

As the drugs of fungal origin have, to a considerable degree, replaced the sulfonamide compounds in general antibiotic therapeusis, experimental studies of combined reagents have in most recent times not included the sulfonamides. However, a few of the results suggest that in some instances the combinations of a sulfonamide with a fungal antibiotic exhibit unusually striking synergistic effects. For example, Klein & Kimmelman (29) concluded that sulfadiazine, when added to streptomycin broth, was far more effective as a synergist and inhibitor of the development of streptomycin resistance by a strain of *Staphylococcus aureus* than was penicillin. It is not inappropriate to suggest that sulfonamide-fungal antibiotic mixtures have not been sufficiently studied experimentally to determine whether or not they might afford special synergistic effects of unusual clinical value, even exceeding that of combined fungal products

In analyzing in some detail numerous experimental studies of the past few years, it is apparent that the effort to appraise all the combinations and permutations of the reagents of the antibiotic field has not been a simple task. Furthermore, the establishment of a basis for broad general conclusions is rendered more difficult by the fact that the test bacterial strain or strains employed by the investigators seemed to account for variable results, sometimes even paradoxical when the *in vitro* and *in vivo* findings seemed inconsistent. However, it is possible to indicate some of the points of special interest which have emerged from the studies as reported up to the present time.

For example the quantities of each of the antibiotics employed in the mixtures was a most important factor in determining the synergistic, antagonistic or negativity of the results. Price *et al* (30) employed *in vitro* and *in vivo* nine antibiotics in various mixtures of two reagents against *Salmonella typhosa* A combination of 20 units of penicillin plus 2 μg of streptomycin proved antagonistic and failed to cure infected mice, whereas 200 units of penicillin plus 1 to 2 μg of streptomycin showed the greatest degree of synergism. These same authors found among their tests with several mixtures, that in only 50 per cent of the trials did the *in vitro* method of testing correlate with *in vivo* tests. Jawetz and associates (25) who have published

and secondary significance involved in the disease processes. It may be noted in passing, that this produces considerable success in not a few instances even if treatment has been given on an empirical basis.

It is of interest to review articles pertaining to the effects of combinations of antibiotics, and to scrutinize the details of the experimental methods and results in order to determine, in so far as is possible at the present time, the effective guidance that may be derived from the laboratory findings as applied to the proper treatment of patients.

Investigators (25, 26) who have dealt with these subjects have defined the terms about as follows:

Synergism exists between two antibiotics when the antibacterial power of the combination is markedly greater than that effected by either reagent alone and is above the summation of the potency of the amount of the single entities contained in the mixture. This applies to observations made both *in vitro*, where the effect is determined by quantitative subcultures of the bacterium-antibiotic mixtures, and *in vivo*, where the survival or death of infected animals (mice) treated with the mixtures represent the end result.

Antagonism exists between two antibiotics when the antibacterial power of either or both of the constituents is greatly reduced below that effected by the dilution factor, or is completely lost Measurements of this interference have been made also by both *in vitro* and *in vivo* techniques. Bliss, Warth, & Long (26) divided their results into the following four categories: (*a*) The activity of an antibiotic may be unchanged (no effect); (*b*) it may be impaired (antagonism); (*c*) it may be improved, but only to the extent of expected combined effect (additive); (*d*) it may be greater than that expected from simple addition (synergism).

The fact that combined effects may be significantly different from the action of a single one of the sulfonamides or reagents of fungal origin was first suggested by Ungar (27), who in 1943, reported that the addition of p-aminobenzoic acid to solutions of penicillin increased the antibacterial action against *Bacillus subtilis* 60-fold, and against a strain of *Staphylococcus aureus* two- to three-fold, but the mixture had no effect when a strain of β-hemolytic streptococcus was used as the test organism. When sulfapyridine, in quantities below the effective level, was added to the solutions of penicillin, the antibacterial effect was greater against *Staphylococcus aureus* and was considerable against *Streptococcus hemolyticus* (Beta type). The same synergistic effect of p-aminobenzoic acid and penicillin, and sulfapyridine plus penicillin, was observed in the combined treatment of mice infected with the test strains of *Staphylococcus aureus* and β-hemolytic streptococcus In 1944, Bigger (28) reported results indicating that in *in vitro* experiments, sulfathiazole enhanced the growth-inhibiting power of penicillin against both staphylococci and hemolytic streptococci to a greater degree than either sulfapyridine or sulfanilamide added to penicillin

It is interesting to note that even before penicillin became generally available for widespread public use, and during the period when new sulfonamide

deals with the particular antibiotics which exhibit either of the phenomena, when the experimental conditions just commented upon have been fulfilled. The combination of antibiotics which has been most uniformly observed by most investigators to exhibit *synergism* is penicillin plus streptomycin. However, as previously noted, Price and associates (30), employing *Escherichia typhosa* as the test organism, found that penicillin plus streptomycin in certain quantitative ranges were antagonistic. Nichols (31) found that when penicillin in 25 per cent of minimal lethal concentrations was mixed with streptomycin in 33 per cent of an effective dose, full bacterial effects against a strain of *Staphylococcus aureus* occurred *in vitro*. Concerning antagonism, chloramphenicol plus penicillin have appeared to yield the interference type of effect with greatest regularity.

Jawetz concluded that it was not uniformly possible to designate pairs of drugs as synergistic or antagonistic as a generality and that the results depended on the qualities of individual strains of individual species. However, among those drugs tested there were two relatively distinct groups. Group I consisted of penicillin, streptomycin, bacitracin, and neomycin. They acted synergistically with one another provided the test organism was, to some degree, susceptible to each member of the pair when tested alone. The members of Group I have never exhibited antagonism to one another. Group 2 consisted of aureomycin, terramycin, and chloramphenicol They have not exhibited either synergism or antagonism when mixed with each other, but sometimes appeared to have an additive effect When one of the drugs of Group I was mixed with one of those of Group 2, the outcome depended upon the previously determined effect of the member of Group I on the test organisms; if highly sensitive to Group I, the addition of Group 2 yielded antagonism; if resistant to a Group I, the addition of a Group 2 exhibited synergism.

The experimental details which have influenced the occurrence of antagonisms between antibiotic drugs may be summarized about as follows (not necessarily confirmed or corroborated by different investigators): (*a*) The quantity of each drug in the mixture and their quantitative ratio to each other in the mixture is of first importance; (*b*) Antagonism is believed to be unilateral between two reagents, i e., one acts unfavorably with the second one but the second does not affect the first Example: chloramphenicol may interfere with action of penicillin but penicillin does not interfere with chloromycetin, (*c*) Antagonism is believed to be based on the bacteriostatic action of one drug, which by preventing multiplication of the bacterial cells nullifies the effect of the second drug, the action of which requires bacterial growth The experimental details which have influenced the occurrence of synergisms between antibiotic drugs may be summarized about as follows (not necessarily confirmed or corroborated by different investigators): (*a*) The quantity of each drug in the mixture and their quantitative ratio to each other in the mixture is of first importance; (*b*) At least one of the pair of drugs must show measurable antibacterial action alone; (*c*) Maximal

most extensively on this subject, have called attention to several interesting features of the significance of quantitative relationships In antagonistic effects performed *in vitro* that involved penicillin, when the other drug, aureomycin or terramycin, was added in an amount too small to exert an antibiotic effect of itself no interference with penicillin occurred; also, when aureomycin or terramycin were used in quantities that were strongly bactericidal, they failed to interfere with penicillin. It may be seen, therefore, that the range of interference was found to be sharply restricted. They concluded that a ratio of penicillin-aureomycin mixtures of 12 to 1 showed interference in several different amounts of total dosages. However, chloramphenicol in a wider range of concentrations interfered with penicillin.

Similarly in synergistic combinations, Jawetz and associates (25) found in quantitative studies, that at least one of the antibiotics of the combinations must exhibit some degree of bactericidal power when acting alone, although the second component may have no effect alone. There was no synergism when both increments were used in subinhibitory concentrations and maximal synergism occurred when both drugs were employed in concentrations that alone showed only bacteriostasis or a slowly acting bactericidal action. Bliss, Warth & Long (26) in bacterial growth studies demonstrated antagonism only when both the reagents were present in relatively high concentrations. They also found that when the reagents were combined in more than one proportion varying results were obtained.

In summarizing the findings mentioned above, it may be noted that in order to obtain manifestations of either synergism or antagonism the experimental results are conditioned sharply by the quantities of each antibiotic employed, and also the amounts of each in relation to the other. Furthermore, the factor of quantity varied depending on whether or not the experimental tests were performed by the *in vitro* or *in vivo* methods. Subsequent reference will be made to these conditions when considering practical clinical usages.

Another experimental factor has been the species of bacteria used as the test organism. Even individual strains of the same species have not been found to behave uniformly Jawetz and associates stated that both synergism and antagonism varied with two strains of the same species and concluded that the response of bacteria to drug mixtures cannot be regularly predicted but is characteristic of individual strains. The same group of investigators found that against two species of bacteria, the same pair of drugs may act antagonistically against one and synergistically with the other. They ascribed this type of result to variations in the susceptibility of resistance of the individual strains to one or the other of the drugs. It is difficult to escape the conclusion, as pointed out by the investigators in this field, that results are highly individualized according to the behavior of the test bacterial strain. This experimental condition will be referred to again in connection with evaluating its significance in clinical therapy.

Within the synergistic and antagonistic categories, still another point

as expressed by Hunter (33) that a total killing power is the required feature of antibiotic therapy—rather than bacteriostasis—in some cases of endocarditis, the special therapeutic successes of streptomycin-penicillin offer clinical support to the rationality of this particular form of treatment.

The combination of aureomycin or terramycin with streptomycin has not, as noted by Hunter (33), been as successful as the streptomycin-penicillin combination.

Continuing with a consideration of selected clinical reports, Ahern & Kirby (37) effected cure of a patient with bacterial endocarditis by combining penicillin with chloramphenicol, the combination which has most frequently exhibited antagonism in experimental trials Although the patient had received penicillin therapy intermittently for three years, the disease had not been cured even though the infecting strain was not resistant. The patient's organism was not highly sensitive to chloramphenicol alone. However, *in vitro*, the chloramphenicol-penicillin exerted a high degree of bactericidal action, and proved to be curative in the treatment of the patient.

Against the background of the detailed requirements that have proved necessary in order to demonstrate the antagonisms and synergisms, it is perhaps useful to illustrate how obscure these several experimental conditions become in the course of the treatment of a patient, a hypothetical example of which may be cited as follows: An adult has typical pneumococcal lobar pneumonia involving one lobe His therapy consists of 300,000 units of penicillin administered intramuscularly every 12 hr. In addition, 1 gm. of chloramphenicol is administered by mouth as a first dose, and thereafter 250 mg every 6 hr. In translating the experimental findings of antagonism of the chloramphenicol-penicillin to this patient, one needs to consider the following points. The size of the inoculum of the experimental procedure is represented by all the viable pneumococci within the involved lobe of consolidation The concentration of penicillin that comes in contact with the pneumococci of the involved lobe is that amount absorbed into the general circulation from the site of injection and subsequently diffused out of the circulation into all areas of the involved lobe. At the same time, the chloramphenicol enters the general circulation following absorption from stomach or intestines and subsequently diffuses from the circulation into all areas of the infected lobe. The rate of absorption of each antibiotic is different; their concentrations in relation to each other in the circulation are consistently changing; their relative concentrations within the infected lobe where they make contact with the pneumococci is entirely fortuitous and in all probability constantly changing It appears, therefore, that in order for the exacting experimental conditions of antagonism for these two antibiotics to be fulfilled in the patient the greatest possible improbability exists.

In the treatment of patients, the closest approach to fulfilling the conditions for demonstrating synergistic or antagonistic effects might be found in local areas of infection where the antibiotics are introduced directly in the proper quantitative relationships that fulfill the estimated requirements in

synergism is derived by employing in the mixture, quantities of each increment that are only moderately antibacterial, rather than in highly potent concentrations; (*d*) Whereas antagonism appears to be a nonreciprocal unilateral reaction, synergism is more readily explained as a reciprocal bilateral phenomenon, with each increment contributing to the summation but differing qualitatively from the essential action of the single antibiotic acting alone.

In the practical clinical field, the literature contains many articles dealing with the simultaneous administration of multiple antibiotics to patients. They are chiefly in the form of case reports, the predominant number of which are concerned with instances of bacterial endocarditis which have either proved refractory to penicillin or have relapsed after treatment has been discontinued The results have usually been successful which justified the publication as a source of informative experience to the profession at large.

In contrast to the successful outcome of the treatment in the reported cases previously mentioned, Lepper & Dowling (32) concluded that the combination of penicillin and aureomycin was not desirable in the treatment of pneumococcal meningitis and ascribed the unsatisfactory results to the interference of aureomycin to the action of penicillin according the antagonistic effects previously reviewed in this article.

Up to the present time the most conspicuously successful combination of antibiotics in practical therapy has been penicillin plus streptomycin. The documentation of the penicillin-streptomycin actions and effects, both experimentally and clinically, has an orderly consistency. Hunter (33) described a patient infected with a penicillin resistant streptococcus who was successfully treated with penicillin and streptomycin. Since then, he and other investigators have explored the subject more extensively Robbins, and Robins & Thompsett (34) in five patients with endocarditis found what appeared to be a causal correlation between *in vitro* summation of the bactericidal action of penicillin plus streptomycin against cultures of the infecting organism and the rapid and permanent cure of the otherwise refractory infection in the patients.

The combination of penicillin and bacitracin have received favorable clinical reports in the treatment of refractory cases of bacterial endocarditis. Their combined use has been based on the synergistic type of *in vitro* action noted by Bachman (35) against cultures of alpha and gamma streptococci Eagle & Fleischman (36) also found that bacitracin plus penicillin eradicated *Treponema pallidum* infections in rabbits with effective therapeutic levels of each below that required for either one employed alone. One of the points of special interest with respect to the penicillin-streptomycin mixed action from a biological point of view is that against some strains of streptococci, streptomycin alone has no effect on the growth curve and exposure to penicillin leaves viable organisms The mixture, however, causes rapid and complete killing of the whole bacterial population. On the basis of the concept

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relation to the properties of the infecting microorganism. It may be concluded, therefore, that in spite of the excellence of the investigations concerned with the actions of multiple antibiotics employed simultaneously, when applied clinically to varying types of infection with different bacterial species present in the areas of disease in varying numbers, neither the unfavorable effects of antagonism nor the desirable advantages of synergism can as yet be predicted. This point has been repeatedly emphasized by the investigators studying the problem.

When interpreting the results in patients, attention should be called particularly to body factors of resistance, both cellular and humoral, and general and local, which play a significant part in the outcome of infectional diseases and are not regularly measurable but none the less are of special significance. The investigators in the field of antagonisms and synergisms have made interesting contributions to the second phase of antibiotic effects mentioned at the beginning of this article. One may await with interest future inquiry into the actions and effects of three or more antibiotics operating simultaneously.

DISEASES OF THE GASTROINTESTINAL TRACT[1]

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In reviewing publications of the past year which were concerned with disorders of the digestive tract, the primary problem of the writers has been the selection of articles for analysis which would appear to contain some new or unusual information relative to the subject under discussion. Doubtless we have over emphasized some subjects, and we may have omitted some which we did not see because they were published in journals which did not come to our attention. However, we believe this review will prove beneficial to its readers.

This year the outstanding contributions to medical literature in gastroenterology are concerned with the very important problem of peptic ulcer. It has been noted that: (*a*) There is a marked tendency to depart from the concept that peptic ulcer is primarily a psychosomatic disease. (*b*) Reports tend to prove that the secretion of pepsinogen (pepsin formation) is under the control of adrenal gland hormone stimulation and consequently the endocrine glands play an integral part in the causation of peptic ulcer activation. (*c*) Evidence has been presented which strongly suggests that a dietary deficiency leads to an absence of some essential antipeptic ulcer factor which plays a role in the genesis of peptic ulcer (*d*) It is likely that the specialized forms of diets and almost all the widely accepted forms of medicinal therapy play no specific role in the healing of peptic ulcer. Also a great deal of interest continues to be expressed regarding the hormone therapy of ulcerative colitis, the diagnosis of chronic recurrent pancreatitis, and the diagnosis and treatment of hepatic disease.

Esophagus

Only two reports on disorders of the esophagus have been reviewed The first deals with the results of medical treatment of idiopathic cardiospasm (1). The authors studied a series of 72 patients between 1932 and 1950) Two methods were used for forceful divulsion of the cardiospasm, or achalasia first, a metal dilator of the Stark type (this instrument contains blades which can be pressed open and thereby stretch an orifice) and second, dilatation was by means of an air bag No anesthesia or sedation was used. Relief of symptoms was obtained in 59 patients (82 per cent) after the first dilatation. Six additional patients were relieved after a second dilatation and four more after a third procedure A total of 69 patients (95 per cent) were ultimately relieved by forceful divulsion Thirteen patients did not return for follow-up studies, but the remaining showed an average of 3 8

[1] The survey of literature pertaining to this review was completed in October, 1952.

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the effect of large oral doses of belladonna and its alkaloids and the intramuscular use of hexamethonium iodide in a small group of patients with duodenal ulcer. He determined the effect of these medications on interdigestive gastric secretions. He found the results to be the same as those in a group of 16 vagotomized patients which were described in the current medical literature. It is to be noted that the author's doses of the drugs used were larger than those usually employed therapeutically in clinical practice.

Three reports on the secretion of pepsin by human stomachs are of particular interest in the consideration of the relationship of the formation of peptic ulcers to excessive secretion of the adrenal gland Janowitz & Hollander (7) studied the basal secretion of pepsin in 61 individuals and measured the amount of pepsin and acid secreted over a 3 hr. period They studied 26 control subjects who were free of gastrointestinal lesions, in addition to 21 patients with duodenal ulcer, four patients with gastric ulcer, and one patient with a gastric carcinoma. They found that the patients with duodenal ulcer secreted on the average, about three times as much pepsin per hour as the controls and that the gastric ulcer patients and the one with gastric carcinoma fell within the normal acid and pepsin range. They noted a high degree of positive correlation in the increase in hydrochloric acid secretion per hour with the pepsin secretion per hour in the duodenal ulcer cases.

Another article on pepsin secretion studies is concerned with the effect of vagal resection on patients with duodenal ulcer (8) The authors note that it is generally accepted that most individuals who have undergone a vagotomy for duodenal ulcer have at least a temporary decrease in the amount of gastric secretion and in the degree of free hydrochloric acid, but that there are no known studies of the effect of this operation on pepsin secretion. They carried out gastric analysis of both nocturnal secretions and secretion during insulin induced hypoglythemia for volume of juice-free hydrochloric acid present and amounts of pepsin produced Thirty-one hospitalized patients with a diagnosis of active duodenal ulcer served as the subjects for this study Fifteen of these patients had had the operation of vagotomy only. They found that they were able to verify that the vagotomy produced a diminution in the volume of gastric secretion and in the amount of free hydrochloric acid, but found no statistical difference in pepsin values per unit volume of gastric secretion in patients with active duodenal ulcer and those in vagotomized patients who had had active duodenal ulcer

In the third report (9), the authors reported a simplified method for determining the excretion rate of uropepsin, as the flow of pepsin in the urine is parallel to that in the stomach and is considered to be under hormone control mediated through the adrenal cortex. The authors recorded not only the technique of the method but also showed marked changes in uropepsin content of the urine which occurred when ACTH was injected therapeutically. The rise in uropepsin values over a period of four days reached a peak of over five times the normal values and dropped back to within the normal range in a 48 hr. period. The method used utilizes the well-known activity

years lasting benefit. It was noted that x-ray examination of the esophagus still showed abnormal findings despite the lack of symptoms present. Delario (2) has reported on a review of the literature of carcinoma of the esophagus This review covered a series of 824 cases who had died. In studying the effects of treatment of carcinoma of the esophagus the author found: (a) the average life of untreated patient without operative intervention was very short, 75 per cent of the cases having died within one year of the time that diagnosis was made; (b) the results of recent methods of surgery, when a radical, surgical resection was carried out, are very good compared to cases having no surgical treatment at all. A small series of cases showed a survival rate of 44 per cent up to two years after the initial operation; (c) results of radiation of therapy have been more successful, having a survival rate definitely higher than those without any definitive form of treatment.

Gastric Physiology

A group of authors have reported their studies of the influence of carbonated waters on gastric emptying time (3) It has been stated that carbonated beverages will hasten the emptying of the stomach. This effect has been said to be due to a reaction between sodium bicarbonate and gastric acidity with the liberation of carbon dioxide The water which was studied by the authors was free of mineral salts They noted its effects on the evacuation of standard test meals in human subjects and found that it ordinarily caused a marked hastening of gastric evacuation which was evident even as early as 15 to 30 min. after injestion.

Bachrach *et al.* studied "more than 50 patients" kymographically after insertion of an air inflated rubber ballon into the stomach in order to measure intra-gastric pressure changes (4) They found.

(a) No type of gastric contraction typical of duodenal ulcer patients. (b) Wide variations in the force of the contractions (c) No constant increase in frequency of "hunger" periods (d) Duration of "hunger" periods (20 to 35 min) the same as in normal individuals (e) No distinctive pattern of motility in the empty stomach with duodenal ulcer (f) Usual unawareness of gastric motor activity, suggesting that the pain of peptic ulcer is more likely related to acid concentration than to intragastric tension

Quigley & Louckes (5) studied the effects of complete vagotomy on the pyloric sphincter and the gastric evacuation mechanism They questioned the accuracy of the concept that gastric evacuation is retarded by this procedure because of a reduction in tone and motility of the stomach and the production of some degree of pylorospasm They used the direct inductographic recording technique in 15 trained dogs. The results showed that following a complete vagotomy in the dog, no permanent change occurred in sphincter behavior and that the changes in gastric evacuation which resulted were not dependent on pylorospasm. In order to test the drug effect which might be most similar to the effect of a vagotomy, Riddell (6)

little reduction in free acidity. X-ray studies were repeated in 71 of the patients who had shown excellent symptomatic relief. These studies were made six to eight weeks after starting therapy. In 75 per cent of this group of cases, no ulcer crater could be demonstrated by x-ray, which indicated healing of the peptic ulcer. In reviewing this article, attention should be called to the following facts, (*a*) these patients received a preliminary therapeutic regime for only two weeks before they were designated as "refractory" (*b*) they also received a liberal diet and antacids after meals while on methantheline therapy and (*c*) no x-ray studies were reported until after a total of 8 to 10 weeks of treatment, so that beneficial results on ulcer crater healing time or demonstrated by x-ray cannot be evaluated.

A case of toxic psychosis, following the use of methantheline, has been reported (15). The patient was an individual 39 years old with acute pancreatitis He developed visual hallucinations with atropine as well as when the drugs were administered separately. Although his idosyncracy caused nonfrightening hallucinations at first, without disorientation, by the third day of treatment with 100 mg of methantheline every 6 hr , he developed acute toxic psychotic manifestations Rogers & Gray, (16) have reported on the use of a new parasympatholytic agent, BA5473, in 24 patients with peptic ulcer. Nineteen of these patients showed ulcer craters. All were demonstrated by x-ray to be healed after three weeks of treatment These patients received a liberal diet. The use of other drugs besides the one tested was not mentioned. On doses of 5 to 15 mg of BA5473, four times daily, symptoms were relieved in all cases in 24 to 36 hr The authors recommend further study of the use of this type of drug in the management of patients with peptic ulcer.

Bartels & Eltorm have questioned whether or not a prolapse of the gastric mucosa through the pyloris is a physiological condition or an abnormal one. (17). They studied roentgenologically 240 individuals whom they termed dyspeptic and 42 normal subjects In the dyspeptic group, 44 per cent exhibited a prolapse of the mucosa and in 34 these prolapses were large. Twenty-one of the normal subjects also showed prolapse, which were large in 10 instances. The authors conclude that prolapse of the gastric mucosa through the pyloris is a normal physicological variation

Histopathology of the Stomach

Two interesting reports on the histology of the gastric mucosa have been reviewed. The material on which the studies are based was removed by means of introduction into the stomach of a flexible gastric tube with a lateral cutting knife, controlled by means of a wire Introgastric suction creates a vacuum which draws a fragment of gastric mucosa into the end of the tube which can then be biopsied In the first report (18), the authors studied the normal gastric mucosa in 105 selected subjects varying in age from 18 to 67 years The site of biopsy was the anterior wall of the stomach close to the greater curvature In their study they noted a constancy of histological normalcy The layers of the stomach wall which were removed by this bopsy

of pepsin in digesting a buffered milk mixture which can be readily carried out in the laboratory.

A number of reports have appeared during the past year on the action [illegible] bromide (banthine) on gastric secre- [illegible] the effect of the drug on the gastric secretion of [illegible] Their ages ranged from 21 to 27 years. *He analyzed gastric acidity response and found that a relatively* slight fall in clinical units of hydrochloric acid occurred, with an average drop of *only* 5.7 units. The *higher the original acidity, the greater the fall in* acidity when the patient received methantheline therapy. In a number of *controlled studies on the effect of methantheline and placebos on the stomach* (11) it was found that (*a*) the drug inhibited gastric motor activity and acid secretion in a *relatively* predictable fashion (*b*) *it was not always effective* in conventional doses (*c*) placebos were similar effective, but to a much lesser degree (*d*) placebos *were more effective if they closely resembled the active* drug.

A similar type of study (12) disclosed the same type of findings for normal individuals but patients with ulcer were also utilized. Methantheline, when given orally or parenterally, depressed gastric secretion in all cases *causing* an average reduction of about 40 per cent. The higher the range of gastric acidity, as noted in patients with peptic ulcer, the more marked the drop in acidity which occurred. The excretion of the dye neutral red was also studied and the findings paralleled those of hydrochloric acid secretion. The drop in *neutral red excretion into the gastric lumen following methantheline therapy* was as low as 10 per cent of the original values

A group of authors (13) studied *the effect of methantheline, belladonna,* and placebos on upper intestinal motility by the multiple balloon kymograph recording method. Thirty-one subjects of college age were studied. After the use of methantheline they found (*a*) retardation of gastric emptying time (*b*) decrease *in contractions of the small and large intestine (c) diminution in the volume of gastric secretion. The effect* tended to occur within 15 min. after the administration of 100 mg of the drug and continued for a 4 hr period *at which time the observations were concluded Methantheline* seemed to be more effective than tincture of belladonna in the results noted [illegible] of belladonna was given in a small dose of only 0 4 cc. [illegible] either the synthetic drug or the [illegible] use of methantheline [illegible]

The therapeutic effect of methantheline [illegible] by Winklestein in a rather large series of patients with peptic ulcer (14). He used a dosage of 50 mg , 3 times a day before meals, at bedtime, and once during the night, in the management of 117 patients with what he termed uncomplicated but refractory peptic ulcer. Eighty-seven per cent of these patients obtained symptomatic relief at once and pain as produced by the Palmer acid test was abolished Gastric analysis studies revealed evidence of very

per cent. If surgery was carried out in later weeks for intractable massive hemorrhages, the mortality was 24.4 per cent. The authors conclude,

> Prognosis is at all times most difficult. Each case is a problem of its own which depends on its final outcome on the judgment and skill of the physician and surgeon in attendance or in the organized hemorrhagic team,—conservative therapy is still eminently satisfactory.

The third report (22) emphasizes a combined medical and surgical service approach to the treatment of hemorrhage. Eighty-seven cases were studied with an over-all mortality of 4.6 per cent. X-ray diagnostic studies were carried out during the active bleeding period in 24 cases without apparent ill effect. The fourth report (23) describes two cases of bleeding Meckel's diverticulum which is an uncommon condition. An important ulceration symptom of Meckel's diverticulum is bleeding which occurs in about 30 per cent of cases. In the first case, ulceration was found but no gastric mucosa, and in the other case there was a typical peptic ulcer present. Both cases were reported cured following excision of the diverticulum. It is emphasized that the dark red color of the stool as distinguished from tarry colored or bright red, is suggestive of bleeding from a Meckel's diverticulum.

The fifth report (24) is a case of Boeck's sarcoid in which the presenting symptom was gastrointestinal hemorrhage. The case was presented as one of hyperspleenism with thrombocytopenia caused by sarcoid. The necropsy did not reveal the exact site of bleeding

The sixth report, (25) is a case of abdominal aneurism which ruptured into the gastrointestinal tract. This condition is rare, only 51 cases having been reported. The author's case was a 78 year old colored female who suddenly developed hematemesis, melena, and shock. A ruptured abdominal arteriosclerotic aneurism into the third portion of the duodenum was found. The reviewers have recently seen a similar case of this condition, which also succumbed rapidly to profuse bleeding.

Peptic Ulcer

In considering the predilection of peptic ulcer from the first part of the duodenum, Ogilvie (26) has reviewed the anatomy and physiology of the duodenum and reached the following conclusions referable to its localization there. He states that (*a*) peptic ulcers are found only in those parts of the alimentary tract which are normally exposed to free hydrochloric acid (*b*) all normal men and women secrete free hydrochloride acid but very few, relatively speaking, develop ulcers (*c*) there must be some failure in the local mechanism of protection before the ulcers form He feels that the localization of the duodenal ulcer in such a restricted area results from the immobility of the first part of the duodenum This same lack of mobility is also present in the lesser curvature of the stomach. This immobility permits prolonged contact of acid gastric juice with an acute ulcer once it has developed, and this prolonged contact converts the acute and often superficial peptic ulcer into a

method showed a similar histological picture in all but two cases in which only minor abnormalities were noted. The authors of this report emphasized that in the past, when it was necessary to depend on autopsy specimens, or specimens removed from stomachs in the operating room which had been subjected to clamping, thereby interfering with their blood supply, that a wide variety of histopathological changes were described which indicated abnormalcy; but that their present study indicates that these changes were the evidences of either post mortem injuries or circulatory changes.

In the second report from Australia (19), 552 biopsies on 462 patients were performed in the same way. No serious complications were observed although some gross bleeding occurred in six instances. Biopsy studies on cats' stomachs showed that tissue healing was evident by the third day after the biopsy and by the eighth day almost complete healing of the gastric wall had occurred. Clinically, the same site of the stomach wall was utilized as in the previous report. Although this report deals primarily with chronic gastritis and pernicious anemia, it was noted that in 21 of 29 cases of duodenal ulcer, a normal mucosal pattern was found. Three important groups of cases were emphasized (*a*) Superficial gastritis, which might be symptomatic and tended to heal (*b*) Atrophic gastritis which was chronic, slow to heal, and often accompanied by symptoms when achlorhydria or marked hypochlorhydria was present. Symptoms in this group of patients included flatulent dyspepsia and epigastric tenderness and discomfort, although the gastrointestinal x-ray findings were negative. This type of gastritis usually occurred in females of 35 to 60 years of age (*c*) Gastric atrophy in patients both with pernicious anemia and in subacute combined sclerosis of the spinal cord.

Digestive Tract Bleeding

As in the past, a number of reports of severe gastrointestinal tract bleeding have been published. Six of these have been selected for comment in this review. The first report (20) includes 195 cases observed over a five-year period. Only 13 cases of this group required operation. Surgery was necessary because they continued to bleed despite the usual medical measures. Seven of these cases died of uncontrolled bleeding With four additional deaths, there was an over-all mortality of 5.6 per cent Operative treatment was recommended for four groups of cases as follows: (*a*) when medical treatment is not effective (*b*) when the patient is over 50 years of age (*c*) when the bleeding is from a gastric ulcer, and (*d*) when there are other indications for surgery. The second report (21) is a very much worth while review of the whole subject of bleeding ulcer in which many series of patients treated medically and surgically are discussed and compared. The mortality of all cases of grave hemorrhages medically treated is recorded as 6 9 per cent; of massive hemmorrhage is recorded as 10.7 per cent, and if the patient was over 45 [illegible] rate from massive bleeding varied between 50 and

treatments This series of cases was divided into two groups of 70 patients each. The first was designated as a control group and the patients received the usual normal hospital diet. In the second group the patients received a modified Lenhart's type of diet which is widely used in the treatment of peptic ulcer abroad. Both groups of patients received alkalis, atropine therapy, and olive oil. There was little or no difference in the therapeutic results in the two groups of cases Pain disappeared in the first group in 25 days and in the second group in 26 days, on the average. Epigastric tenderness disappeared after several weeks. The mean time of its disappearance was 30 days for the first group and 37 for the second group. Healing time of the ulcers by x-ray was 58 days in the first group and 64 days in the second group. It was evident that those patients on prolonged bed rest showed more rapid healing than the small group of ambulatory patients. It is concluded that the dietary treatment of peptic ulcer, as practiced at present, does not hasten the healing of peptic ulcer and actually may delay it. In the second of these two papers (32) the author reviews the whole subject of the treatment of peptic ulcer relative not only to special diets, but to other types of therapy which are commonly used and so often considered necessary in the management of patients with this disease. It is pointed out that the therapeutic use of "the certainly valuable remedies" can hardly be justified from our present knowledge and that the onus of proof of their effectiveness is on the advocate of each of the special types of diet and forms of drug therapy. It is emphasized that there are only three procedures which are of proven value: (*a*) Diminishing the gastric acidity by any of various measures (*b*) Gastrectomy (*c*) Neuropsychiatric therapy, which has only a very limited application.

Considerable attention is being paid to criteria by which to determine the rate of healing of peptic ulcer In this respect the importance of crater healing time by x-ray is emphasized by a number of writers Steigmann & Shulman (33) have studied 138 cases of gastric ulcer Every one of these cases was x-rayed weekly or bi-weekly in order to determine the crater healing time From the data presented it is calculated that the healing time was approximately seven weeks (49 days) in the 31 cases completely studied. It varied between 7 and 105 days It is stated that this healing time of gastric ulcers compares favorably with that of peptic ulcers produced experimentally in dogs Two British authors have reported on the "factors influencing the rate of healing of gastric ulcers" (34) They observed 64 cases over a three-month period These cases were x-rayed monthly Half of the group was treated for the first month in the hospital and were subsequently ambulatory, while the second half was ambulatory for the entire three-month period of observation. They concluded that (*a*) hospitalized patients tended to show an earlier relief of symptoms and earlier healing tendency of the ulcer (*b*) The rate of subsequent healing in patients returning home was no more rapid when they had been hospitalized for the first month, than when not (*c*) If the ulcer had not healed to an average of one-third of its original size in one month, it was unlikely to heal in three months (*d*) Controlled trials of phenobarbital and

chronic one. Relative to the genesis of peptic ulcer, a case of gastric ulcer occurring in a patient after lobotomy, has been recorded (27). The patient was a 37 year old male who developed gastric ulcer symptoms about six months after the lobotomy. X-rays taken some two months after onset of symptoms showed an ulcer of the lesser curvature of the stomach close to the antrum. Surgical exploration revealed an indurated ulcer which was benign histologically. The authors suggest a causal relationship between the lobotomy and the development of the gastric ulcer. Kellock (28) discusses in a most interesting way the question of the relationship of mental conditions to the etiology of duodenal ulcer. He notes that at the present time it is commonplace to regard duodenal ulcer as a "psychosomatic illness," caused by psychological stresses and developing in a specific type of personality. He approached this problem by studying the childhood of patients with duodenal ulcer, because of the importance of the genesis of adult personality going back to the childhood environment. His case analysis included 250 persons with duodenal ulcer and 250 control cases, individuals with various other diseases. He studied the factors of family, parental relations, education, childhood, and social class He found no difference between the group of patients with duodenal ulcer and the control group. He concludes—"The possibility that the ulcer personality may be the effect rather than the cause of the disease, must be concluded." In considering childhood and peptic ulcer, Goldsberry (29) has reported a case of gastric ulcer in a five year old boy who had dark stools, abdominal pains, and vomiting. A gastric ulcer was demonstrated by x-ray in the antrum of the stomach. The lesion measured 1.2 cm. in diameter. The author emphasized the rarity of this condition

Palmer (30) has reported on the clinical significance of the small benign gastric ulcer. He has based his report on a study of 100 patients with a small benign lesion of the stomach. He defines these small lesions as not larger than 1 0 c. in diameter, and at least 0.5 cm. in depth Most of the patients were in a hospital under a minimum of four months observation. All but one case was observed for a period of from four months to five years. An analysis of the cases shows that nine per cent of the ulcer was on the greater curvature of the stomach, and in 10 per cent achlorhydria was present after two histamine gastric analyses and an analysis of the gastric juice for a 12 hr. night drainage period In 21 per cent of the cases, there was peptic ulceration elsewhere than in the stomach Important complications developed in 45 per cent of the cases including severe hemorrhage in 30 per cent and perforation in 12 per cent. In 21 per cent of the cases, surgery was carried out for some other reason than the suspicion of gastric carcinoma The author concludes that small benign gastric ulcers are primarily important because of their propensity to severe complications and that the best treatment is not necessarily surgical.

Two reports were published in the *Lancet* with identical titles: "The Treatment of Peptic Ulcer." In the first (31) 140 patients with peptic ulcer were studied to determine the value of medical treatments, especially dietary

interest particularly in relation to the management of peptic ulcer because of its property of inactivating pepsin (37). Before studying its effect on patients, the authors studied its use in a group of dogs in which they were producing histamine peptic ulcer. It was found that the survival time of those dogs under treatment with the detergent was very much prolonged when compared to a control group of dogs. In treating 20 patients with gastroduodenal ulcerative disease, a mixture of sodium alkyl sulfate and mucin was employed. Ten of these patients were so improved during the course of treatment that surgery, which had originally been contemplated, was indefinitely postponed. Also three of ten patients with severe ulcerative colitis showed "spectacular improvement" while on the same treatment. Gastric secretion studies were carried out in a number of cases. It was concluded that the volume of their fasting gastric content, the one-half hour secretory rate, and the total available acidity were all decreased. The concentration of pepsin per cc. of juice and the total available pepsin were considerably diminished. Also the total amount of lysozyme, but not its concentration, was decreased.

A report of the treatment of 100 patients with peptic ulcer with fresh cabbage juice (vitamin U) strongly suggests that fresh vegetable juice contains some factor which promotes the healing of both gastric and duodenal ulcers (38). Four cases of jejunal ulcer were also included. It was found that the symptom of pain was relieved in the average case by the fourth day without any routine form of medication. Ulcer crater healing time as determined roentgenologically, was found to be 13 days on the average for the 54 patients in which it could be accurately determined. This healing time is considerably shorter than that of patients who are treated with the usual standard forms of medicinal therapy, which were not routinely employed in any of the 100 patients reported.

Three cases in which an unfavorable course of gastric ulcer occurred during the administration of cortisone and ACTH have been reported (39) All of these were males. In the first case, an asymptomatic gastric ulcer became symptomatic within ten days after starting ACTH therapy and it increased materially in size in 25 days at which time a second gastric ulcer developed. There was an increased output of hydrochloric acid and also three to fourfold increase in morning basal gastric secretion When ACTH therapy was stopped all evidence of ulceration disappeared within three weeks time. The second case was under cortisone therapy for chronic arthritis After five days of therapy severe abdominal discomfort developed and a huge gastric ulcer was found at the time of x-ray examination. Cortisone therapy was stopped and the ulcer crater healed in three months' time The third patient had a history of recurrent gastric ulcer. On the third day of ACTH therapy, ulcer distress again occurred in this patient and grew more and more severe The acid and gastric secretion output increased markedly. After three weeks of ACTH therapy the ulcer perforated Operation disclosed a large benign ulcer on the lesser curvature of the stomach Postoperative recovery was uneventful

vitamin C treatment did not tend to increase the healing rate of peptic ulcer (e) After one month of treatment, combining both groups, only 8 of the 61 cases showed absence of ulcer crater by x-ray, and after three months only 17 cases were apparently healed as assessed by x-ray examination.

Another report of the healing of peptic ulcer has been made from analyzing 1082 autopsy results on adults (35). This study was undertaken because of the impression that there was a disparity of healed peptic ulcers observed at the autopsy table compared to the number of ulcers diagnosed by clinical means, gastroscopically, and by x-ray, and that healing could be so pronounced at times that there would be no visible or gross evidence that an ulcer had existed. In the 1082 autopsy examinations, there were 54 cases of active chronic peptic ulcer, 18 of which were completely healed. Of the active cases, 50 were in the stomach, 29 in the duodenum, and in five there were combined lesions in both duodenum and stomach. In the healed cases, five were in the stomach and 13 in the duodenum. The incidence of active ulcer was 5 per cent, and of healed ulcer, 1.7 per cent. It is noted that the total incidence of peptic ulcer in this series, including both active and healed, is 6.7 per cent, which is low compared with the incidence in the general population. It is suggested that complete healing of peptic ulcer may occur without leaving any gross or histological evidence that a lesion had been present previously.

A group of physicians reporting on the management of peptic ulcer (36), present a brilliant therapeutic result by means of gastric acid neutralization. The aim of their treatment was the same as that reported by Sippy in 1915—neutralization of free acid In the treatment of 1106 cases of peptic ulcer they employed a liberal high protein diet, antacid mixtures, and gastric drainage at 8:00 A.M to check on the control of acidity. They used two alkaline mixtures: One composed of calcium carbonate and magnesium oxide in milk, which was administered with food; and a second mixture, composed of aluminum hydroxide jell and milk of magnesia administered when the stomach was relatively empty. This second mixture was usually given in a dose of 45 cc. between meals, at 8:00 P.M., bedtime, and at 2-hr. intervals throughout the night. In their series of cases there were only four females. The mean patient age was 38 years with a range of 18 to 82 years. There were 84 patients with gastric ulcer (5 3 per cent). They obtained pain relief within four days in 990 patients. The ulcer crater healing time as determined by x-ray was: for gastric ulcers, 17 days with a range of one to five weeks in 36 cases; for duodenal ulcers, 15 days with a range of one to six weeks in 506 cases. Sixty-nine obstructed patients required surgical therapy and apparently were eliminated from the medically treated series. Their results, as determined by pain relief and the healing of ulcer craters by x-ray, are better than any other reported recently except those cases responding to cabbage juice therapy.

A report on the therapeutic use of sodium alkyl sulfate, a detergent, in the treatment of gastroduodenal ulcerative disease and ulcerative colitis, is of

peptic ulcer cases (43). Approximately 60 per cent of all cases of benign gastric ulcer were operated upon. In 1950 there were 196 cases with an operative mortality of 2 2 per cent During the same year, 453 patients with duodenal ulcer were operated upon. A partial gastrectomy was performed on 81 5 per cent; gastroenterostomy alone in 10 per cent; vagotomy alone in only one patient. Actually only 13 per cent of all duodenal ulcer cases seen were operated upon. A hospital mortality rate for all of the duodenal ulcer cases was 1.5 per cent. Fifty-eight cases of gastrojejunal ulcers were operated upon; 76 per cent by partial gastrectomy, vagotomy alone in 15 5 per cent.

Nuboer (44) discusses the problem of carrying out primary, partial gastrectomy for perforated peptic ulcer. He states that after simple closure by suture of a perforated ulcer, there is a recurrence of peptic ulcer trouble in more than 50 per cent of the patients, including further perforation, hemorrhage, and persistent prolonged medical care for indigestion. The primary mortality is still high. Nuboer operated on 131 cases by primary partial gastrectomy with only a 3.8 per cent mortality. Of the five patients dying, three succumbed from peritonitis, one died under anesthesia and one from an injury to the bile and pancreatic ducts. A follow-up of 108 of these patients a year or more later, showed that 20 were having slight discomfort after meals, but working. One had had a recurrence requiring further resection but all the other patients had no gastrointestinal symptoms of any kind. The author feels that this procedure may give a lower primary mortality and produces a better late result than the simple procedure so commonly employed. A fourth group of cases has been reported (45) emphasizing that vagotomy alone for duodenal ulcer gave poor results, and that vagotomy with the performance of a gastroenterostomy gave excellent results in 68 per cent of the patients in four series of cases operated upon. It was found that vagotomy for patients with gastrojejunal ulcer following gastroenterostomy did not produce satisfactory results However, a vagotomy has produced very satisfactory results when performed for gastrojejunal ulcer occurring after a partial gastrectomy. In discussing this subject, the authors (45) make this final comment

> Tendency of the results in all groups and types of ulcer and combinations of operations is to become progressively worse with the passage of time—a return of acidity to preoperative levels in 26 per cent of cases leads to speculation as to whether results of vagotomy are not temporary.

Golden (46) has emphasized the frequency of obstruction in the efferent loop of the jejunum which follows partial gastrectomy, and that it is frequently of a functional nature, and a result of spasm (46) The symptoms of epigastric fullness, nausea, and vomiting which indicate the development of this type of obstruction usually appear during the second postoperative week. In the majority of cases they disappear in a few days but may last as long as two to three weeks X-ray examination not only discloses retention in the stomach pouch, but also a characteristic picture of spasm in the adjacent efferent duodenal loop The author's figures which accompany the article

Gray *et al.* (40) have written the most informative article to date on the effect of ACTH and cortisone on the stomach of patients with peptic ulcer. Their schematic presentation of the influence of adrenal corticoids on the peptic glands of the stomach should be familiar to everyone. The authors present a series of carefully studied cases of peptic ulcer showing the stimulating effect of ACTH and cortisone on the production of pepsin (and uropepsin) and the subsequent development of peptic ulcer symptoms (even within 24 hr.) and ulceration as demonstrated by x-ray. A reactivation of peptic ulcer pain and the development of hemorrhage and perforation are usually manifest during the second week of hormone therapy, but may occur later. It is noted that patients secreting normal amounts of pepsin into the stomach and excreting normal amounts of uropepsin into the urine may develop very high pepsin values, similar to those encountered in cases of chronic duodenal ulcer, when receiving hormone therapy and that these patients may also form peptic ulcers. This report should be read in its entirety by all physicians who are interested in the peptic ulcer problem. The case of a 45 year old female who was under treatment with cortisone for rheumatoid arthritis has been reported by Moe (41). At the end of the third month of therapy she developed gastric symptoms and an x-ray examination disclosed a gastric ulcer high up on the lesser curvature of the stomach. With cessation of cortisone therapy and the administration of methanthaline in a dose of 100 mg. every 6 hr. the ulcer was demonstrated to have disappeared in 82 days time

A series of four papers on peptic ulcer have been reviewed which deal with the operative management of this disorder. The first, by Sarah Jordan (42) is a report of the subcommittee on surgical procedures in peptic ulcer of the American Gastroenterological Association The results of these studies are divided into two groups, the first dealing with the results of vagotomy, with and without gastroenterostomy, and the second with subtotal gastric resections. Follow-up studies for the average were from two and one-half to three years The results in the first group of vagotomized patients with the added operation of gastroenterostomy were 75 to 80 per cent successful (relief of all symptoms and signs of activity) Those operated on with the single procedure of vagotomy alone, showed only 59 to 62 per cent successful relief. In the second group, operation for duodenal ulcer with or without vagotomy, showed complete relief of symptoms in 85 per cent of cases. In a second subgroup of this group carried out for gastroenterostomy ulceration, there were also 85 per cent excellent results. It is of significance that there was a mortality of 5.4 per cent for gastric resections which includes 25 per cent for acute hemorrhage, and only one per cent for gastroenterostomy with vagotomy, and 1 4 per cent in gastric resection plus vagotomy. The reviewers feel that vagotomy with gastroenterostomy for duodenal ulcer, vagotomy or vagotomy alone for anastomatic ulcers should be reserved entirely for selected complicated cases and that these procedures should be abandoned in the routine management of ulcers, judging from the above report.

The Mayo Clinic has made a similar type of report on their operated

years 1948 to 1950, a total of 62 complete gastrectomies were performed with a mortality rate of only 13 per cent and it is stated that total gastrectomy for malignancies of the stomach should be the aim if feasible. Regional lymph gland involvement decreased the five-year survival rate in gastric carcinoma from 48 per cent without known involvement to 19 per cent with known involvement when complete gastrectomy was performed. The importance of carrying out extensive surgical procedures for this type of malignancy is noted. In another report from the Mayo Clinic (51), it is stated that about 0 5 per cent of all patients seen (more than 100,000 patients annually) have gastric carcinoma. A detailed statistical study is presented both in tabular form and graphically. The present five-year survival rate is 14 per cent and the three-year survival rate is now 18 per cent. The successful resection of a primary suprapapillary carcinoma of the duodenum is reported (52). This patient was a female 46 years of age, with a one year history of upper abdominal pain and fullness after meals. X-ray examination revealed a narrowing and irregularity of the descending portion of the duodenum On operation, an ulcerating polypoid mass, six cm in length, was found between the second and third portions of the duodenum. A modified type of Whipple operation was successfully carried out with excellent immediate postoperative recovery.

Disorders of the Small Intestine

Gold & Sawyer have presented a review of 221 cases of diverticuli of the gastrointestinal tract (53). In this series they discussed 15 cases in which the esophagus was involved; one in the stomach; 64 in the duodenum, one in the jejunum, one in Meckle's diverticulum, and 139 in the large bowel. The relative paucity of symptoms associated with diverticuli of the gastrointestinal tract is emphasized. An unusual case of acute intestinal obstruction due to phytobezoar, which was macaroni, has been reported (54). The authors of this review note that they were able to find only 42 cases of phytobezoar of the small bowel published since 1940. The patient was a 37 year old male who complained of severe abdominal cramps and vomiting His bowel movements had been regular Laparotomy for small bowel obstruction revealed an obstructive lesion in the ileum due to a firm bolus of macaroni, which was removed It is of interest that 15 months previously, the patient had had a Hofmeister type gastrectomy for intractable gastric and duodenal ulcers.

Jacques (55) has reported, on the basis of his experiment with rats, that pantothenic acid may relieve paralytic ileus He treated 16 patients successfully The dose which he used was 50 mg of the calcium salt per cc. intramuscularly. Usually one dose was sufficient but occasionally two or three doses were necessary before relief was obtained. Occasionally, the therapeutic effect was dramatic with the passage of much flatus and the development of striking clinical improvement.

Appendicitis has received relatively little attention in the medical litera-

illustrate this nicely. It is of the utmost importance not to confuse this form of postoperative functional obstruction with an organic obstruction, and thereby carry out further surgery which is unnecessary.

TUMORS OF THE STOMACH AND DUODENUM

A report on studies of the exfoliative cytology in the diagnosis of gastrointestinal malignancy presents some interesting diagnostic data (47). It reviews a number of recently reported papers, and calls attention to the fact that cancer of the gastrointestinal tract account for more than 40 per cent of carcinoma deaths in the United States. In carcinoma of the esophagus, a biopsy diagnosis is preferable but in about one-half of the cases, a careful cytological study of the sediment will result in a positive diagnosis. In 100 cases with carcinoma of the esophagus there were three falsely reported positives. In studying stomach secretions, when a gastric abrasive balloon is employed, there is approximately a 75 per cent correct positive diagnosis. With duodenal drainage in approximately two-thirds of the patients with carcinoma of the gall bladder, bile ducts or pancreas, exfoliated, well-preserved malignant cells may be found so that a correct positive diagnosis is made. It is noted that this method may give twice as many positive diagnoses as x-ray examination. In malignancy of the colon and rectum, a 75 per cent or greater positive diagnosis is possible from cytology studies The lesions low down in the bowel are readily diagnosed Those higher up are frequently not.

Dolan & Sherman have discussed hypertrophy of the gastric mucosa (48). They emphasize: (*a*) that hypertrophic gastritis is primarily inflammatory, is not primarily a hypertrophic condition, and may heal (*b*) that gastric mucosal hypertrophy implies pathologically a mucosal overgrowth and is not a reversible condition; and (*c*) that mucosal polyposis presents "an adenomatous pattern" which is readily differentiated from the other two conditions. In an attempt to differentiate between benign and malignant diseases of the gastric antrum, the comparative value and limitations of gastroscopy in the diagnosis of gastric disorders has been studied (49). Considerable interesting statistical data is presented in comparing gastroscopic findings with x-ray findings in patients with benign and malignant gastric ulcerations and in so-called antral gastritis It is stressed that in 30 patients with gastric carcinoma of the antrum, gastroscopy suggested malignancy in two-thirds of the cases. If carcinoma is only suspected by the x-ray findings, gastroscopic examination cannot be depended upon to rule out a lesion even when one is not identified. When the pylorus is clearly visualized by the gastroscope and no definite lesion is found, malignant disease of this area is very unlikely. Carcinomatous ulceration of the antrum may not be visualized by gastroscopic examination.

Walters *et al.* discuss advances in the surgical treatment of cancer of the stomach (50). It is stated that in modern surgery there is an increase in number of total gastrectomies being performed for gastric carcinoma. In the

The Mayo Clinic has presented a well-documented report on the gastrointestinal lesions of periarteritis nodosa (60). The study includes 30 cases observed between 1926 and 1944 in which postmortem examinations had been performed; 26 of these patients presented abdominal symptoms and signs. The findings are divided into four case groups. In the first, there were 18 cases in which there was a history of gastrointestinal symptoms and necropsy revealed definite abdominal lesions. In the second group, there were five cases in which histological lesions were identified in the gastrointestinal tract but no gross lesions were found within the abdomen. In group three, there were three cases in which there were no digestive tract symptoms but lesions were found at post mortem in the gastrointestinal tract. In these cases the periarteritis seemed to be confined to the arterioles of the submucosa. There were four cases in the fourth group in which no gastrointestinal tract lesions were found. As a rule, the pathological lesions were well-distributed throughout the gastrointestinal tract involving the liver, gall bladder, pancreas, and mesentery. It was noted that abdominal pain was the most prominent clinical symptom and occurred in 70 per cent of the cases. When abdominal pain was generalized the lesion most commonly found, which might account for the symptoms, was mesenteric thrombosis An unusual case of ileocecal tuberculosis with target cell anemia has been recorded by McCabe (61). The patient was a 49 year old negress with an ulcerohyperplastic form of ileocecal tuberculosis, thought to be primarily in the digestive tract, as chest x-rays studied were negative and there was no positive evidence of tuberculosis elsewhere The target cell anemia which was present before operation, cleared up completely after the surgical resection of the tuberculous lesion.

Five reports on the treatment of sprue have been reviewed Three of these are relative to the use of vitamin B_{12} in the treatment of this condition and two are relative to the use of cortisone and ACTH therapy In the first, the therapeutic effect of the oral administration of vitamin B_{12} in the tropical form of the disease, was studied (62). Ten patients received vitamin B_{12} medication orally. Three of these patients were also given gastric juice along with this vitamin. The results obtained were. (*a*) B_{12} orally has definite but limited activity (*b*) the simultaneous administration of gastric juice potentiated the effect of vitamin B_{12} in two of the three cases (*c*) small doses of vitamin B_{12} (5 to 15 μg. daily), produced a poor response (*d*) very large daily doses of vitamin B_{12} (150 to 200 μg daily), were required to produce a satisfactory clinical response (*e*) vitamin B_{12} given intramuscularly and the administration of folic acid orally and intramuscularly, were much more effective in treatment than vitamin B_{12} orally (*f*) it was concluded that the use of vitamin B_{12} orally in the treatment of sprue is not the most effective or practical form of treatment for this condition.

The second report (63) describes a case of sprue with severe anemia in a 40-year-old white male in New York. He was treated both orally and intramuscularly with large doses of vitamin B_{12} and failed to respond Folic acid

ture during the past year. However, four cases, occurring in one family have been recorded (56). All were in children, two age six, one seven and one twelve and one half years. In one case, threadworms were thought to be a causative factor. In one there was a catarrhal appendicitis, and in the other two infection played a prominent part. All patients made an uneventful recovery.

The question of an abnormal roentgenological small intestine pattern because of vitamin deficiency has been made the basis of a report in middle-aged and old individuals (57). The small bowel pattern was studied in 20 patients with normal thiamin blood levels and 20 patients with hypothiaminemia. In neither group was there any significantly abnormal intestinal pattern except for three possible exceptions in the second group which were considered thiamin deficient. However, the authors of this report conclude that the absence of a definite deficiency pattern in their series of cases, does not indicate that an abnormal pattern would not occur in more severe grades of deficiency such as those associated with beri beri.

The roentgen findings in cases of ileojejunitis have been reported in which the process was a chronic granulomatous form resembling terminal ileitis. The diffuse continuous type, and the interrupted type which involves all or most of the small intestine are included (58). Forty-five cases were studied and divided into two groups relative to the character of the x-ray findings. In the first group, comprised of 38 patients, the disease occurred in a nonstenotic form. The x-ray features were blunting and thickening of the mucosal folds, and in the more advanced cases, a cobblestone reticulation and cast form of picture was noted. Occasionally, pseudo-diverticuli developed and in rare instances, a finger print-like defect In the second group, in which there were 11 cases, stenosis of the bowel was a feature In this group the x-rays showed long areas resembling rigid pipes with proximal dilatation There were also skip areas, tumor masses and fistuli formation in this group. The differential diagnosis of ileojejunitis has to be made from lymphosarcoma and tuberculosis of the small bowel

A group of authors have reported on the long term results of the surgical treatment of regional ileitis (59). They present their findings after a seven-year follow-up of 137 surgically treated cases In this group of cases the patients had been observed from 9 to 21 years. They noted that many patients had enjoyed long periods of good health, indicating excellent palliation from the procedure, rather than cure. They state that "no other form of therapy has so much to offer for so long a period of time." They found that for the operation of ileocolostomy the mortality rate was zero, while the recurrence rate was 23 per cent, and for resection the mortality rate was 14 per cent with a recurrence rate of 46 per cent. The late recurrences showed a distinct tendency to spontaneous healing However, the comment is made "that in recent operations in which resection was carried out, the results seemed to be more satisfactory and might be more applicable to the surgical management of cases of regional ileitis in the future."

the cases studied were of the chronic advanced type. In 15 patients receiving ACTH in doses which varied from 40 mg. to 200 mg. daily, there was objective clinical improvement and marked improvement in the diarrhea in nine cases. In six additional cases there was only subjective improvement with no improvement in diarrhea. In three cases, sigmoidoscopic examination revealed marked improvement in the abnormal condition of the intestinal mucosa. In 12 cases there was a recurrence of symptoms including diarrhea shortly after cessation of treatment and in three instances it was noted that there was an exacerbation of the mucosal lesions of the rectum and sigmoid. There were serious complications of treatment in three patients. These complications were coronary thrombosis, perforation of a duodenal ulcer, and perforation of the colon. Patients who were treated with cortisone did not benefit very markedly. It was noted that cortisone was far less effective in that only one of five patients showed any clinical response even on daily doses up to 150 to 250 mg. In a second report on the use of ACTH in the treatment of chronic ulcerative colitis, cortisone was thought to be of little value in the treatment of patients with chronic advanced forms of the disease or in cases already in remission (69). It was found to be most effective in cases of short duration in which there was a relatively small amount of damage to the colon, but with severe systemic symptoms present. There was little evidence that ACTH had any direct curative effect upon the disease in the colon but it was suggested that small doses taken over long periods of time might provide some protection against exacerbations of colitis activity. In a third report, the effect of adrenocorticotropic hormone on the fecal lysozyme titer was analyzed (70). This study was an attempt to clarify the significance of the presence of excessive amounts of lysozyme in cases of active ulcerative colitis. The results of this study indicated that lysozyme production was a secondary manifestation of the disease and not of any etiological significance. This conclusion was based on the lysozyme studies in 30 normal individuals, 24 patients with the acute phases of the disease, and 29 patients with a chronic inactive form of ulcerative colitis. A marked and rapid fall in lysozyme titer occurred with successful ACTH treatment of ulcerative colitis which was interpreted as reflecting only a nonspecific tissue reaction to injury.

In the fourth report, the effect of ACTH therapy in six cases of ulcerative colitis and in two additional cases of regional enteritis was reported (71). It was found that in the acute phase of ulcerative colitis a definite and even dramatic remission often occurred. Diarrhea was usually under control within two weeks and [illegible]

lar favorable clinical results occurred All but two cases treated relapsed in two to nine months but they responded to further ACTH or cortisone treatment. ACTH treatment was carried out in the cases reported for an average period of four to eight weeks.

therapy orally in large doses (70 mg. daily) initiated an excellent clinical response with complete disappearance of the diarrhea and the anemia. In the third report, six patients with active tropical sprue were studied (64). The effect of combinations of folic acid and vitamin B_{12}, when the dose of each had little or no hematopoietic activity, were studied. A combination of a small dose of folic acid (1 67 mg.) and a small dose of vitamin B_{12} (25 μg) was tested orally for its therapeutic effect in each of the six patients. Usually a good clinical response was obtained which was comparable to the response to parenteral liver extract therapy. The conclusion was that the macrocytic anemia of sprue and of pernicious anemia is the result of a multiple deficiency and that both folic acid and B_{12} are necessary, that they probably exert some synergistic action, and that folic acid is essential for the absorption and utilization of vitamin B_{12}. The therapeutic effect of cortisone and ACTH on tropical sprue have been reported in a series of five patients (65). These patients were designated as having primary sprue, which is described as a disorder of fat metabolism Each had been sick for one or more years and four of the patients had proven resistant to the conventional forms of sprue treatment. Four patients received ACTH and all showed an improvement in their well-being and an increase in appetite In all four diarrhea disappeared and the stools became formed. There was no marked weight gain. Steatorrhea tended to persist but at times the fecal fat content approached normal. A vitamin A tolerance test showed evidence of improvement in two cases. The hematological findings remained unaltered These cases relapsed within a few days to two weeks after treatment ceased. The one case treated with cortisone showed a similar therapeutic response but with a better weight gain after prolonged treatment. There was direct evidence of improved fecal fat absorption The tendency to relapse was also marked following cortisone therapy. In a fourth report the effect of cortisone therapy on nontropical sprue was noted (67). Extensive clinical studies of six cases of idiopathic steatorrhea were described and metabolic balance data were obtained in two of these cases Results were: (*a*) Cortisone produced a definite subjective and objective improvement in every case. The stools decreased in number and approached normal in appearance. Appetite and strength improved. The abdominal cramps and distention completely disappeared (*b*) Cortisone proved equally effective therapeutically when given orally or by injection (*c*) The improvement in the stools, with a decrease in their fat content, occurred coincidentally with the return of the prothrombin time to normal in the patients studied (*d*) It was thought that the improvement in these patients was attributable to more efficient intestinal absorption (*e*) It appears that cortisone therapy offers the most effective means of treating sprue during exacerbations of the disease.

Four reports dealing with the effects of ACTH and cortisone therapy in the management of ulcerative colitis have also been reviewed in detail. In the first the clinical effects of ACTH were studied in a group of 15 cases and in an additional group of five cases which received cortisone (68). Twelve of

years, because in six (or 9 per cent), carcinoma developed (*c*) Evidence of pronounced fibrosis or stricture formation of the bowel (*d*) Chronic arthritis (as the author states, "practically all cases will improve after iliostomy and colectomy") (*e*) The surgical complications of perforation and of bowel obstruction. A three-stage operation is advocated on the basis of an experience in 50 cases so treated with a mortality of 6 per cent for the iliotomy or for a subtotal colectomy and 0 per cent for the final rectal colic excision.

Two reports on the association of idiopathic ulcerative colitis and pregnancy have been reviewed (75). In the first, a careful study of 19 patients, hospitalized for ulcerative colitis, was carried out In this group the patients had been pregnant at least once. In 15 of these cases, the colitis had had no effect on the pregnancy. In five cases the colitis had improved, in four cases the colitis became worse. In six cases the colitis started with the onset of pregnancy, particularly in the first trimester In the post partum period, a remission in the colitis occurred in three cases and a relapse in five cases. It is noted that the course of ulcerative colitis in pregnancy is unpredictable and that the effect of the previous pregnancy on the course of colitis is not a reliable guide for its effect on the subsequent one It is concluded that it is better for the patient to remain nonpregnant unless she is in a long time remission. The second report (76) deals with an analysis of ulcerative colitis in 16 patients with 22 pregnancies. The cases were divided into three groups· (*a*) Eight with active symptoms, although none of the fulminating type (*b*) three in remission and (*c*) five in which the colitis developed during pregnancy. In group one, four patients felt that they had improved with pregnancy, three that the disease was aggravated, and one that no effect had occurred In the second group, two patients thought that they had been unaffected and one thought she was worse In the third group all five patients became acutely ill. One became quiescent, one died with a miscarriage at six months, one had no viable child, and two patients remained active clinically so that in the post partum period, one required an iliostomy and one developed an arthritis The opinion is offered that pregnancy occurring in an inactive stage of ulcerative colitis is usually well tolerated, while ulcerative colitis developing during a pregnancy "is an extremely virulent disease and may be fatal "

Pancreatic Disease

One group of workers (77) tested the possibility of use of the antithrombin titer as a guide in the diagnosis of acute pancreatitis This study was based on their observation that in dogs alterations of the antithrombin levels have produced severe shock-like states with hemorrhagic phenomena, elevated amylase, as well as hypocalcemia and hyperlipemia. In 50 of 55 cases of acute hemorrhagic pancreatitis, they found marked elevation of antithrombin titers For a control series they tested the antithrombin levels of 304 patients with acute surgical abdominal states Ten were found to have elevated titers. Three of these had acute gall bladder disease and four were

Two cases of ulcerative colitis have been reported from India which responded to vitamin B_{12} therapy (72). They were treated with vitamin B_{12} by injection, 20 mg. daily for one week and then 20 mg. twice a week thereafter for three weeks The first case was a female of 34 with moderately severe anemia. Clinically, she was relieved of symptoms and was without diarrhea after one week of treatment. After three weeks her blood count had returned to normal. A follow-up sigmoidoscopic examination revealed a normal appearing bowel wall. The second case was a male of 52 years of age with a slight degree of anemia. The same excellent therapeutic results were obtained. Both of these cases presented a sigmoidoscopic appearance of idiopathic ulcerative colitis. Morrison has reported on a series of cases of ulcerative colitis treated with salicylazosulfapyridine (Salazopyrin) (73). Fifty-two patients with the chronic form of this disease were treated over a period of two and one-half years. Thirty patients improved to such a marked degree that symptoms were definitely relieved after three days of therapy on the average, and there were only three stools daily on the average. The average number of stools daily before treatment had been nine. Eighteen per cent of the patients showed an intolerance to the drug which was administered in a dose of 1.5 gm. every 3 hr. day and night, for two weeks. With the plan of drug therapy employed, there was then a rest period of two weeks and then the previous course of treatment was repeated once or twice. The author's treatment results for three groups of patients can be classified as follows: (*a*) drug intolerance, 18 per cent (*b*) no response, 24 per cent (*c*) improved, 58 per cent. Of the patients which had improved, 20 cases showed great improvement, while 10 cases relapsed after treatment with one or two courses of the drug. It was found that the sigmoidoscopic picture improved parallel with clinical improvement and became worse parallel with relapses of the colitis. The author concludes that only about one-half of the cases improved, with a tendency to relapse without treatment which is marked, and feels that there is a need for a more desirable preparation in the treatment of this chronic disease The reviewers have treated over 100 patients with the agent in a dosage of 1 gm , four times a day, and obtained superior results to those of the author. With this smaller therapeutic dose only three patients have had toxic symptoms which interfered with their treatment. It is particularly noteworthy that with relapses, when patients have been taken off therapy, there is an almost 100 per cent uniform favorable response when drug therapy is resumed. Many of the patients now under treatment have continued on salicylazosulfapyridine therapy in a dose of 1 gm., twice a day for one or more years without further relapse.

A report on the surgical treatment of chronic ulcerative cholitis lists five indications for surgery of this condition (74). These indications are: (*a*) Failure of medical treatment which is characterized by persistent relapse (*b*) Pseudopolyposis on the basis of clinical and x-ray evidence which is considered an absolute indication for a major surgery. This positive statement is based on the author's series of 68 cases treated surgically during the past 10

but also that stimulation of the pancreas by feeding was necessary if the lesions were to appear (82). The present study showed that an excised duct and piece of duodenum lying freely in the peritoneal cavity lead to the development of fat necrosis The authors found that this occurred because no adhesions formed in the presence of the duodenal mucosa although they were regularly formed over the pancreatic duct when it was not attached to its duodenal mucosa. They found that in experimental animals the prompt formation of adhesions over the pancreatic duct or traumatized area of pancreas were sufficient to prevent a generalized fat necrosis.

The clinical features of chronic pancreatic disease have been reviewed in relation to alcoholism (83). A relationship statistically between alcoholism and pancreatic disease was established. It was found that individuals receiving alcohol intravenously did not develop any increase in pancreatic secretion. The oral ingestion of alcohol caused local spasm and edema of the duodenal mucosa. It was suggested that alcohol orally caused the pancreas to secrete a large volume of pancreatic juice which flowed against an obstruction of the distal duct (or ducts) caused by spasm and edema of the ampula and papilla secondary to the effect of alcohol locally. The fact that alcohol causes an increase in the volume of pancreatic juice when given orally and does not do so when given intravenously, and the previously shown effect of alcohol as a topical agent on the duodenal mucosa causing edema, spasm, and increased tonus of the sphincter, suggest that the local effects as an irritant are of prime importance. The possibility that certain patients with chronic pancreatic disease are afflicted with a hereditary disorder was raised (84) The details of a family pedigree in which the hereditary transmission of chronic relapsing pancreatitis was a feature is presented It was presumed that this transmission was due to an autosomal dominant gene. A case of chronic relapsing pancreatitis with associated hyperlipemia was presented (85) it was considered that the hyperlipemia was probably of familial origin. This phenomenon antedated the appearance of chronic pancreatitis. The attacks of chronic pancreatic disease were well controlled by dietary means It was suggested that in such cases the hyperlipemia might be the cause of chronic relapsing pancreatitis

The occurrence of aberrant pancreatic tissue was reviewed. It was found in 14 per cent of 410 autopsies (86) The authors noted that 80 per cent of such aberrant growths were found in the duodenum, usually in the second portion Their x-ray and gross appearance is that of nodular polyp-like growths The association of such tissue with varying degrees of indigestion was considered. The syndrome of annular pancreas which constricts the second portion of the duodenum or the pyloric segment of the stomach was also reviewed.

The appearance of jaundice during a seizure of relapsing pancreatitis often casts doubt on a precise diagnosis The not infrequent recurrence of this state has been discussed (87) and the findings in six cases reviewed. Two unique findings often associated with carcinoma of the pancreas are (*a*)

found to have an acute alcoholic gastritis Two patients who had empyema of the gall bladder and one with a perforated peptic ulcer were included in this group of 10. The authors assumed the presence of an associated pancreatitis in these cases. The degree of accuracy which this study appears to show indicates that this test of pancreatic dysfunction will compare very favorably with serum amylase determinations in patients in the acute phase of this disease. These same authors report their experience in the use of plasma antithrombin determinations in the study of patients who were jaundiced because of carcinoma of the pancreas (78). They performed antithrombin tests in 261 jaundiced patients. They found marked elevation in 11 patients with carcinoma of the pancreas whose jaundice was of less than four weeks duration, and normal levels in six patients with carcinoma of the pancreas whose jaundice was of between one and six months duration. In those patients with carcinoma of the pancreas and jaundice of over six months duration low antithrombin levels were described. They were able to show that there were no significant elevations in patients who were jaundiced for other reasons. The early appearance of antithrombin elevation is coincident with the period of most favorable operability and the authors suggest that the early use of this procedure may prevent a deleterious delay in surgical procedures on such patients.

Another report emphasizes that the rather early fall of the amylase level in many patients wtih acute hemorrhagic pancreatitis has limited the usefulness of this diagnostic test when the patient is first seen in the third and fourth day of his illness (79). This early decline in the amylase level was noted in studies of the calcium, phosphorous, magnesium and amylase levels in 27 patients with acute pancreatitis. It was found that hypocalcemia occurred in 19 of these 27 patients usually in the second to fifth day of illness. It would appear that the blood calcium level would be of considerable diagnostic help in those patients seen late in an attack. The secretin test for pancreatic disease of a chronic nature was reviewed (80). The diagnostic difficulties presented by this disorder were emphasized by studies which showed that in 10 proven cases of chronic pancreatic disease, only three patients were found to have an abnormal response after the administration of secretin and methacholine (Macholyl) as carried out in the standard test. It was noted that a dose of secretin in vagisected men gave a full enzymatic response. The effect of insulin hypoglycemia on pancreatic secretion stimulated by secretin was studied in this same group of cases. There was no enzyme production by the pancreas in response to this stimulus. It was found possible to produce experimental pancreatitis in dogs, cats, and monkeys by the administration of ethionine, according to the clinical and histological features of the experimental disease produced in this way which resembled those found in the end results of an acute attack of the disease in man (81). The experimental production of acute pancreatitis with fat necrosis was described by workers who had previously shown that the development of fat necrosis depended not only on enzyme digestion following the severance of the pancreatic duct

in 15 cases. Of the four in whom the visualization was not considered normal, 3 had some degree of gall bladder shadow, and only one complete non-visualization. The result of this study would only appear to be of value in those cases of infectious hepatitis in which jaundice was minimal.

The benzoin and shellac turbidometric liver function tests have been reviewed. Modifications of these tests were suggested by a group of workers who found that the number of abnormal tests in the control group was high (95). In 20 of 67 normal controls there was a positive reaction in the case of shellac. The relationship of the alkaline phosphatase blood level to the degree of serum bilirubin elevation was studied in four patients (96). Serial observations showed that with an early partial biliary obstruction a rise in the bilirubin was not necessarily accompanied by a rise in the alkaline phosphatase. However, with the release of the obstruction or a continuing rise in the serum bilirubin there always occurred an elevation of the alkaline phosphatase which might persist even when jaundice had cleared. With increasing jaundice of prolonged degree and liver damage, the serum bilirubin might continue to rise but the alkaline phosphatase could still remain the same or fall. In such cases improvement with relief of the biliary obstruction caused the alkaline phosphatase level to rise

The difficulties of predicting fatal cases of hepatic insufficiency have been discussed (97). Thirty-two patients dying of liver failure were studied by means of a wide variety of liver function tests No specific alterations were encountered in the result of these tests which would separate them from those of individuals who had nonfatal hepatic insufficiency.

New modes of transmission of homologous serum jaundice have been described (98). Twenty-two cases of this disease were collected in which the virus has been transmitted apparently by the use of human thrombin as an hemostatic agent during surgical procedures One death occurred One-third of these cases occurred during neurosurgical use of the material. The artificial transmission of viral hepatitis by the communal use of syringes by heroin addicts and morphine addicts has again been noted (99, 100). A careful study of an epidemic of infectious hepatitis in an orphanage has been reported (101) Over a period of eight years 72 student nurses and three other adults developed infectious hepatitis It was established that the nurses contracted the disease from the children. Icterus among those children under three years was quite rare It was shown that the epidemic was not air borne, nor spread by food or water. Infection apparently occurred by direct fecal-oral transmission and the outbreak was abolished by enforcing standard aseptic technique

The use of ACTH and cortisone in acute homologous serum jaundice has been described in four patients (102). Those in an acute phase of the disease who were treated with these two agents enjoyed a prompt defervescence of symptoms and subsequent symptomatic relief However, in two instances clinical relapse followed discontinuation of the therapy. A further remission was obtained following a renewal of the use of these agents. It is noted that

multiple venous thrombi, and (*b*) abdominal and back pain aggravated by the supine position. A large series of proven cases of carcinoma of the pancreas were investigated to determine the statistical occurrence of these two complications (88). In this study it was noted that 22 per cent of patients with carcinoma of the pancreas developed multiple venous thrombi at some phase of their illness. The aggravation of the abdominal pain by supine position and its relief by erect position was noted in 43 per cent of such patients.

Liver Disease

Numerous reports outline the information that one may obtain from needle biopsy of the liver. The attempts at correlation of findings of the tissue pathologist with the liver function tests of the clinicians have been reviewed in two papers (89, 90). The most consistent observation is the close correlation between bile plugs in the canaliculi seen on histological section and the clinical evidence of an elevation of serum bilirubin. The association of periportal inflammation and periportal fibrosis with an elevated serum bilirubin were also clearly shown. It was noted that changes in the liver cells themselves were slight in the large majority of biopsies, and that these changes could not be correlated properly with any abnormal liver function tests. The value of liver biopsy in the diagnosis of sarcoid has become apparent from a review of a large series of cases of this disease (91) in which needle biopsy of the liver was performed. It was found that there was histological evidence of sarcoid in 76 per cent of the cases biopsied. The usual lesion described was a focal granuloma.

The development of the liver biopsy technique over the past decade and its wide general use have established criteria for the indications and contraindications for its use. A hitherto undescribed complication of this procedure has been reported this year (92). Needle biopsy of the liver was performed on a jaundiced patient who died 7 hr later All sections of lung tissue which were obtained showed bile pigment in the capillaries. It was concluded that a fatal bile embolism had occurred following this procedure, and that the hazard of needle biopsy of the liver in the jaundiced patient is far greater than in the nonicteric person.

The early appearance of bilirubin in the urine may be used to establish the diagnosis of infectious hepatitis one to three days prior to the appearance of clinical jaundice (93). The presence of the abnormal pigment in the urine may enable the clinician to develop his diagnosis early in the course of the disease if the possibility of an acute hepatitis is considered. The x-ray visualization of the gall bladder has been proposed as a test of liver function in patients with slight icterus It has been used for this purpose in the differential diagnosis of cirrhosis of the liver and an acute infectious hepatitis (94). The authors of this report found no normal visualization of the organ in any group of patients with cirrhosis. In a group of 19 patients with infectious hepatitis and slight icterus there was normal visualization of the gall bladder

Various diets of potato starch, glucose, and yeast were used to produce hepatic necrosis in animals (110). Alpha tocopherol and methionine prevented the development of the experimentally produced necrosis. Two groups of authors report the occurrence of fatal hepatic necrosis during therapy of epilepsy with phethenylate sodium (111, 112). The hepatic changes followed prolonged therapy with the drug. The use of gamma globulin in the protection of susceptible individuals during an epidemic of infectious hepatitis was reviewed by Stokes and others (114). These authors were able to study three epidemics in different institutions and found that human gamma globulin was able to protect susceptible individuals for at least five-, eight-, and nine-month periods. They suggested that subclinical infectious hepatitis may have occurred during some declining phase of the protection rendering the treated individuals immune at a later date.

The effect of repeated phlebotomies in hemochromatosis is described in an interesting communication by Rous & Arrowsmith (115). The authors considered that the development of hemochromatosis results from a defect in the normal iron barrier occurring in the intestinal nucous membrane They were able to study three patients in severe phases of the disease by means of liver function tests and aspiration biopsy of the liver. Because the only way to remove excess iron from the liver and other organs is by removing hemoglobin, they bled their patients repeatedly over many months In one patient they removed 50 l of blood in a 60-week period They described the restoration of blood by such patients as remarkable Improvement in the liver function tests of these patients was clearly shown Also they demonstrated a decrease in the amount of iron in liver tissue obtained by serial biopsy and a coincident diminution in liver size. A note of caution in the use of hepatic artery ligation for the treatment of chronic liver disease was sounded by Rosenblum & Egbert (116), who described a case of liver necrosis and death following this procedure They compared tissue taken before and after the procedure and found ischemic infarction of the liver nodules had occurred following ligation.

A new cholecystographic medium, iodopanoic acid (Telepaque) (117), was used in observations of 100 patients with suspected gall bladder disease. The authors believed that the side effects following the ingestion of this dye were considerably less than those in the same group which were later studied with iodoalphionic acid (Priodax). (The clinical experience of the reviewers casts doubt on this statement.) They were able to show an increase in number of gall bladders which could be visualized, increased density of the gall bladder shadows; more adequate response to the fatty meal, which afforded a better means of studying the evacuation phase, and also an increased incidence of visualization of the common bile, cystic, and hepatic ducts. The incidence of infection in chronic cholecystitis was determined both by cultures of duodenal drainage material as well as bacteriological findings at surgery (118). The authors observed in this series of 259 cases that there was little difference in the symptoms experienced by the patients with sterile gall bladders and those with infected gall bladders. They noted that the

one of the patients progressed to a typical phase of chronic hepatitis despite this therapy. It was considered that the sense of well-being and good appetite brought on by these hormones accounted for the evidence of clinical remissions that were noted.

The effects of diet on fatty infiltration of the human liver were studied in a series of 17 alcoholic patients (103). It was noted that the feeding of a basal diet of 75 gm of protein, 250 gm. of carbohydrate, and 75 gm. of fat had significant lipotropic effects in 13 patients. The ingestion of large amounts of choline by four patients who were already on the basal diet, did not produce any additional lipotropic effect compared to those patients who were on the diet alone. The radioactive isotope P^{32} has been used to measure the rate of phospholipid turnover in humans (104). Twenty hospitalized patients who showed clinical and laboratory evidence of advanced liver disease were studied by this means. It was found that a large dose of choline given to patients with fatty infiltration of the liver which had been proven by biopsy caused a substantial increase in the phospholipid metabolism. Similar large doses in normal controls did not cause such an increase. In patients having cirrhosis without fatty infiltration and in patients with uncomplicated infectious hepatitis the rate of phospholipid exchange was not stimulated by choline or methionine. The role of the adequate diet as a means of therapy in liver disease was brought out in animal studies (105). Both necrotic and fibrotic changes which were produced in the livers of experimental animals were found to be completely reversible by the institution of a proper diet.

The histological appearance of liver tissue removed from 62 patients who died of various complications of peptic ulcer has been reviewed (106). The authors are unable to find any conclusive evidence that hepatitis or cirrhotic changes in the liver were caused by peptic ulcer. The influence of virus hepatitis on the morphology of the gastric mucosa was reviewed in another paper. One hundred patients with acute infectious hepatitis in various phases of the disease underwent gastroscopy, and biopsy of the gastric mucosa. The tissue removed was compared with that from 100 normal controls. It was found that there was apparently no more evidence of disease in the gastric mucosa of those patients with infectious hepatitis, than in those of the control series (107).

Cholangiolitic biliary cirrhosis was studied by careful liver function tests as well as by needle biopsy and at necropsy (108). The principal clinical studies relative to this disease were the elevation of the direct bilirubin and total cholesterol, and high alkaline phosphatase levels which varied from 23 to 121 Bodansky units. The authors placed xanthomatous biliary cirrhosis in this group of cases. The principal histological change was described as pericholangitis. It was suggested that parenchymatous cellular disease was secondary to these bile duct changes. An unusual case of cirrhosis of the liver which developed from a severe brucella hepatitis was documented by repeated histological study of surgical specimens of the liver as the disease progressed (109).

advanced to support this contention (125). The suppression of the intestinal bacterial flora is desirable in many instances, particularly in preoperative preparation of the bowel. Sulfonamides remain in general use although their efficiency is not great. The broad spectrum antibiotics have certain inherent disadvantages because of their systemic action. Further, the broad spectrum drugs often allow the continued development of pseudomonas (pyocyaneous) and proteus microorganisms. Mixtures of polymyxin, neomycin, and bacitracin by mouth were described as more effective suppressing agents (126). These offer advantages over both sulfonamides and broad spectrum antibiotics because they are highly efficient, give no demonstrable blood level or systemic signs, and afford broad bacteriological inhibition. The mixtures were effective for long periods. It has been suggested that the prothrombin time of humans is related to the activity of the intestinal flora, and there has been suspicion that the broad spectrum antibiotics which interfere and suppress this growth may prolong prothrombin time. The authors of one paper studied 18 patients who were on terramycin for a period from three to five days during preparation for removal of carcinoma of the colon or rectum. It was noted that the prothrombin time was not altered during this period to terramycin therapy in the 18 patients studied (127).

Because of the rather benign course of the infection in many patients, bacillary dysentery due to *Shigella alkalescens* is not a reportable disease in many states One group of authors feel that the disease should be treated as a true bacillary dysentery despite the fact that the course is usually mild. They point out that in children and in some adults, severe infections may occur. Unusual clinical features associated with infection from this organism are the rather common involvement of the urinary tract and the occasional occurrence of a positive blood culture (128). Organisms which have not previously been considered potent pathogens have assumed an increasing importance as the causes of general systemic infection arising during the course of treatment with antimicrobial drugs A comprehensive review of bacteremia as a result of gram negative bacilli other than the salmonella was presented by Waisbren (129) in a study of 29 such cases. The commonest portal of entry was the genito-urinary tract and the commonest precipitating factors were catheterization and instrumentation. Ten of these cases had bacteremia because of *Escherichia coli* Seven were from *Aerobacter aerogenes*, and 5 from *Pseudomonas aeruginosa* There were five male patients with bacteremia from the proteus organism. Two distinct clinical pictures were seen In one the appearance was that of great toxicity, in the other a shock-like state Combinations of antimicrobial substances were often used rather than single drugs The apparent malevolence of proteus bacilli in this series of cases is noteworthy. The relatively high resistance of this species to most antibiotics suggests that severe infections as a result of this organism may increase in frequency

Three patients with intestinal tuberculosis demonstrable by x-ray and other clinical findings were treated with *p*-aminosalicylic acid, for from four

incidence of cholelithiasis was the same in both groups. The occurrence of cholecystitis in childhood was again brought to our attention by authors who describe a child of 13 with calculous cholecystitis and common duct stones (119). The authors cite two cases of this disease which occurred in children who died with undiagnosed obstruction of the common duct from stone.

The carcinoma of the right colon is reviewed by an author who described 242 cases encountered between the years 1930 to 1950 (120). Twenty-one of these patients or 10 per cent died postoperatively in the hospital. One hundred and twenty enjoyed a five-year survival, while 52 were alive and well after five to ten years following surgery. Fifty-one of the group, about one fifth, died of recurrent carcinoma. The occurrence of carcinoma arising in adenomas of the colon and rectum was considered on a statistical basis by a group of investigators who were able to study 265 adenomas (121). In this series of cases, 39 showed carcinomatous changes. There were 10 carcinomas wherein a residue of benign adenomatous tissue was found histologically. The proctoscopic findings in 5980 proctoscopies were presented in two categories by Diamond (122). He performed 5100 proctoscopic examinations on nonalcoholic individuals and found that 3.3 per cent of females, and 5.5 per cent of males had adenomas of the rectum or sigmoid. In 820 alcoholic patients he found an incidence of 12 per cent of adenomas of the rectum and colon in females, and 18 per cent in males. This fourfold increase in incidence of adenomas in alcoholic individuals has not been described before and there is no general clinical impression that carcinoma of the rectum or colon are more apt to develop in alcoholics than in nonalcoholics The author raises the point that if a majority of adenomas undergo malignant changes over the years, alcoholic patients are far more likely to have carcinoma of the rectum and colon than normal individuals. Two odd fungating lesions of the rectum and sigmoid colon have been described in the current literature (123, 124)). One was a nonspecific granuloma of the rectum and sigmoid colon in the form of lesions which clinically simulated carcinoma but which responded to therapy with aureomycin. The other was a polypoid endometrioma of the colon, a rare state which closely simulated a carcinoma of the colon Endometrial tissue infiltrated the wall of the colon and presented as a polyp in the sigmoid which overlay the mucosa and underwent ulceration When the lesion was resected, endometrial tissue was found in the regional lymph node.

The value of the broad spectrum antibiotics in the treatment of intestinal infections has been rather well worked out in previous years One of the most annoying complications of such treatment has been the development of

[illegible]

clinical evaluation of the patient, stool cultures, and cultural evidence was

stool at the end of a seven-day period. One group of the treated patients were then given six 0.25 gm. bismuth glycolylarsanilate tablets one time each week. This prophylactic treatment held the reinfection rate to 25 per cent. In another group receiving two 0 25 gm. tablets per day, the reinfection rate was 10 per cent. Bismuth glycolylarsanilate has proven to be an outstanding drug in the therapy of human amebiasis. However, in this past year a case of agranulocytosis occurring (138) during antiamebic therapy with the drug was reported. The bone marrow recovered when the drug was stopped.

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to six month periods, at a dose of from 12 to 16 gm. per day. Toxic reactions did not cause discontinuation of the drug in any of the three. There were striking clinical and radiological evidences of improvement at the end of this time (130). Although the development of pseudomembranous enterocolitis is usually associated with a preceding operation on the intestine, a group of authors reviewed 14 cases of the disease which were not preceded by surgery. The clinical picture was that of sudden onset of severe abdominal pain, profuse watery diarrhea, and collapse. Five of their cases were associated with heart disease and five with intestinal obstruction due to carcinoma Of the four others secondary to miscellaneous causes three were associated with various infections (131).

Because of the increasing age of the American population there is a natural increase in the frequency of diverticulitis. A general review of this problem (132) indicated that the majority of these cases were best handled by means of conservative medical treatment and antibiotics. The authors believe that fistulous complications of the disease require colostomy before surgical correction of the fistulae. They have found it possible to do an end to end resection of the sigmoid colon where a diseased segment must be removed if there are no fistulous complications. Gastrointestinal allergy is represented by the case of a 26-year-old man who was operated on after several attacks of severe, crampy abdominal pains. At surgery a thick bowel consistent with that of regional ileitis was discovered but the histological picture showed a massive edema with an intense eosinophilia. It was later determined that this allergic phenomenon was due to seafood (133). Previous literature contains suggestions that the colic of lead poisoning may at times give rise to an intestinal volvulus but the evidence has never been more convincingly presented than in a report of five cases of lead poisoning (134) in which an intestinal volvulus developed. In four cases, the volvulus was in the sigmoid colon and in one instance the small bowel.

Severe paroxysmal abdominal pain in 31 children was associated with an abnormal electrocardiogram pattern in 30 cases. Nine of these children had experienced frank convulsions (135). The authors considered these abdominal crises to be part of an epileptic phenomenon of cerebral origin.

Quinacrine hydrochloride is reported as an effective agent in the treatment of *Taenia saginata* infection in humans. Thirty-four patients with known infestation were treated with this material followed by a brisk saline purge. All expelled live worms within 2 hr , twenty-one with the scolex. The follow up stool studies were negative In contrast to these outstanding results in the treatment of tapeworm infestation the author reports disappointing persistence of *Hymenolepis nana* (136)

In an institution where there was a known high incidence and exposure to *Endameba histolytica*, trials of drug prophylaxis of amebiasis was attempted (137). It was determined that 55 per cent of the inmates had amebae in their stools. Ninety-three per cent of a group treated with bismuth glycolylarsanilate (Milibis) and chloroquine (Aralen), developed a negative

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DISEASES OF THE CARDIOVASCULAR SYSTEM[1]

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Coronary Heart Disease

Physiologic as well as anatomic studies have contributed to an understanding of coronary heart disease during the last year. The problem of whether or not the shock-like syndrome following infarction results from toxic substances or hemodynamic factors has been dealt with by Freis and associates (1) and by Agress *et al.* (2). Freis and associates found that myocardial infarction resulted in a reduction of cardiac output and an increase in total peripheral resistance, central venous pressure, and circulation time. They found a slight reduction in total blood volume. Apparently infarction results in a reduction in stroke volume because of the myocardial injury. A series of compensatory mechanisms then follow, which produce a clinical picture resembling shock. Congestive heart failure following myocardial infarction is the result of intensive vasocontriction existing in the presence of a reduced stroke volume, resulting in fluid retention. In contrast, Agress and associates found that in artifically produced myocardial infarction in dogs there was a total blood volume loss of 20 per cent.

Investigation of coronary blood flow in man using the method of coronary sinus catheterization and the nitrous oxide method have shown a marked increase in coronary blood flow in anemia (3, 4, 5) In hypertension the coronary blood flow was normal, indicating an increase in the coronary vascular resistance. In mycoardial failure, the coronary blood flow and the myocardial oxygen consumption per unit of heart tissue were normal, and digitalis appeared to have no direct effect on coronary blood flow. The clinical impression of the value of inhalation of 100 per cent oxygen in coronary infarction has been confirmed by experimental work, using polarographic determinations of the local oxygen availability in dog's ventricular muscle during coronary occlusion (6) The authors differentiate, according to the electrode response during coronary occlusion, three myocardial zones One a central [illegible]

inhalation during coronary occlusion results in a prompt rise in the electrode readings characteristic of normal muscle in the outside area The rise in oxygen tension in the central area is only slight, while in the border area one third of the initial fall is usually regained. Unquestionably, therefore, in-

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and the blood supply is mainly from a deficiency in the latter. Under the general heading of coronary insufficiency, he distinguishes heart strain ("myocardial failure in which the muscular fibers, in attempting to respond to an excessive load, stretch and lengthen beyond the physiological limits"), asymptomatic coronary heart disease, the anginal syndrome, the intermediate coronary syndrome, and finally the myocardial infarct. The intermediate coronary syndrome denotes a condition similar to that which Blumgart and his associates have termed coronary failure (12). In a more recent report, Blumgart (13) correlates clinical-pathological findings with the physiology of the coronary circulation. Similar to Graybiel, Blumgart states that the underlying physiologic mechanism of angina pectoris, coronary failure, and acute myocardial infarction lies in the relative disproportion between the requirements of the heart for blood and the supply through the coronary arteries. He stresses the importance of bedrest following myocardial infarction because necrosis of the muscle is the important feature of the first week and removal of the necrotic muscle and replacement by connective tissue predominates during the next five weeks He believes that large infarcts are usually not completely healed until two to four months have passed.

In contrast to Blumgart's conservative treatment of coronary infarction, Levine (14) believes that strict bedrest is injurious to the patient with acute coronary thrombosis. The patients were kept in a chair rather than in bed for increasing portions of the day, beginning not later than the first week after the attack. Levine believed that there were no complications attributable to the chair treatment. It is interesting that, in discussing Levine's paper, Dock agreed with Levine's point of view but stressed the fact that the patient who is in shock needs to be in bed with his feet higher than his shoulders

Since Herrick's clinical description of coronary artery occlusion, more and more cases of coronary occlusion belonging to the younger age group have been described. Ledy (15) mentioned that there is a pathological condition occurring in infants which produces a physiologic condition similar to arteriosclerotic coronary artery disease He described four cases of coronary occlusion and myocardial infarction in young males and quoted extensively from the literature on the subject of coronary artery disease in young adults. It is well known that in women the incidence of coronary thrombosis is rare However, Robinson (16) points to the frequently demonstrated predilection of diabetic women to coronary atherosclerosis. His data suggest that approximately one of five women with coronary thrombosis was a diabetic, and that a diabetic woman is 14 times as likely as a nondiabetic woman to suffer coronary thrombosis

The incidence of thrombo-embolism in acute and healed myocardial infarction was studied in a series of papers (17, 18). The Mayo Clinic workers studied the incidence of intracardiac mural thrombi and the various factors which influenced their formation They found a greater incidence

halation of high concentrations of oxygen can reduce the extent of muscle necrosis resulting from coronary occlusion.

Anatomical studies have also contributed to a better understanding of the mechanism of coronary heart disease. Using the injection of radio-opaque lead agar, the effect of anemia, cardiac hypertrophy, valvular heart disease, coronary heart disease, and cor pulmonale on the formation of coronary collaterals was studied (7). Anemia was found to stimulate the development of intra-arterial coronary anastomoses. In cardiac hypertrophy, the frequency of anastomosis was high. This is in agreement with physiologic findings (3, 4, 5). In valvular disease the coronary anastomoses were numerous. In recent coronary artery occlusion, the incidence of collaterals was relatively low as compared to the incidence of anastomoses directly distal to old occlusions. Apparently the time interval between the occurrence of the occlusion and death was insufficient in some instances for the development of compensatory anastomoses. Anatomical findings may be misleading, however, because the finding of collateral blood vessels is not sufficient proof of sufficient blood flow through these vessels. This problem was also discussed by Wiggers (8). He deals in detail with the work of Prinzmetal (9) and concludes that in normal dogs the collateral supply of the surface layers of the heart is not adequate to maintain contractions of sufficient force to prevent the ventricular wall from stretching in the effective region. It is highly improbable that any better functional supply could develop in human hearts, which have demonstrably poor collateral channels Wiggers advances the idea that there is no support for the belief that any drug can penetrate connecting collaterals in normal hearts. He also warns against the indiscriminate use of drugs which, by elevation of the aortic pressure head plus dilatation of subsidiary coronary circuits, are supposed to act favorably in forcing blood through collaterals. He mentions the well known fact that drugs such as pressor amines, epinephrine, nor-epinephrine, etc , increase the work of the heart, elevate pulmonary pressures, and tend to induce ventricular arrhythmias. In clinical-pathological correlations based on a detailed history of the patient and post-mortem studies, Zoll and co-workers (10) found that not a single patient with angina pectoris in the entire series was free of heart disease. All patients with the disease had either valvular or hypertensive heart disease, and 90 per cent of them had coronary narrowing or occlusion.

The final impression gained from these physiologic and anatomic studies remains that coronary insufficiency is a patho-physiologic state in which the blood supply is insufficient to meet the demands of the working heart. It makes no difference whether this insufficiency in the blood supply is brought about by dynamic or pathologic anatomical factors Graybiel (11) speaks of a relative and absolute coronary insufficiency, relative meaning the insufficiency existing when the discrepancy between work of the heart and the blood supply is mainly from hypertrophy of the muscle; absolute insufficiency develops when the discrepancy between the work of the heart

the treatment of coronary occlusion with myocardial infarction set up by the American Heart Association. This committee has recommended that the employment of anticoagulant therapy in patients with this disease, unless contraindications to anticoagulant therapy exist, is of paramount importance. Russek *et al.* (25) believe that it is neither necessary nor desirable to administer bishydroxycoumarin to patients with acute myocardial infarction who qualify as good risks according to the criteria used. The evidence indicates that, in such instances, anticoagulant therapy requires accurate laboratory determinations of prothrombin activity and daily testing until the dosage is standardized. Sampson (26) feels that the continued use of bishydroxycoumarin (Dicumarol) for months or years may be beneficial in patients with a tendency to frequent episodes of myocardial infarction. Tromexan, [ethyl bis(4-hydroxycoumarinyl) acetate], an anticoagulant drug with more rapid action and excretion, has been also studied by Sampson and found to have a nearly complete absorption effect in 12 to 24 hr. and an excretion rate of about 80 per cent in 24 to 36 hr. However, it requires the same precautionary daily determinations of prothrombin activity as bishydroxycoumarin. The dosage is approximately five times that of bishydroxycoumarin and is more costly at present. The action of tromexan has also been studied by Burke & Wright (27). An evaluation of the comparative actions of these drugs was recently reported (28) Tromexan works faster but appears to protect against thromboembolism to a degree which parallels that of Dicumarol. Anticoagulant therapy seems to have a place in the preventive treatment of myocardial insufficiency. Smith & Papp (29) describe the results in 14 patients who present a prodromal coronary syndrome, treated by heparin and bishydroxycoumarin. In seven instances such treatment coincided with progressive improvement; in six of these no infarction developed, and in the seventh the ensuing infarct was slight, although previous infarction had been severe. Unquestionably, the prodromal syndrome is hard to define, and consequently the results are difficult to evaluate.

Results on the use of khellin obtained during the last year are conflicting Scott & Seiwert (30) gave patients alternate placebo and khellin. They believe that the patients receiving the drug experienced fewer anginal attacks, but side effects were frequent. Apparently, purified crystalline khellin produces fewer side effects than do khellin mixtures Kleiber (31) thinks that experiences with the drug are sufficiently encouraging to deserve further study Other studies pertaining to the use of khellin were performed by Osher and co-workers (32) and by Dewar & Grimson (33)

Efforts to elevate the pressure head in the aorta to combat the shock-like syndrome following myocardial infarction have already been discussed (8). Most authors agree that the use of pressor substances in myocardial infarction should be approached with caution. However, there is no question that these substances have some value Miller & Baker (34) administered *l*-arterenol intravenously to seven patients with recent myocardial infarction

of left ventricular mural thrombi in acute infarction as compared to healed infarction, and found a greater incidence in anterior infarction. Other factors leading to thrombi were congestive failure, cardiac hypertrophy, and enlarged hearts. Stasis of blood is believed to be the greatest single factor in the production of thrombi.

In addition to the usual symptoms of coronary infarction, cerebral manifestations such as syncope, convulsions, coma, or hemiplegia may be the the only presenting symptoms of acute myocardial infarction (19). Some patients have no symptoms except for dyspnea after myocardial infarction (20). Complete absence of pain during acute cardiac infarction was observed in 7 out of 150 cases. Acute paroxysmal dyspnea was the main symptom Of the patients observed 3.3 per cent had complete heart block during the attack. It is believed that prognosis in cardiac infarction without pain and complicating heart failure is serious (20).

The differential diagnosis between acute coronary thrombosis with myocardial infarction and acute pulmonary embolism is at times difficult. The electrocardiogram may be greatly misleading in the differential diagnosis between the two conditions. Levine & Vazifdar (21) emphasized a unique medical-legal problem arising from the difficulties in the differential diagnosis between coronary infarct and plumonary embolism.

The incidence of myocardial infarction in a rural hospital was described by Harrison (22). The author described 236 cases of myocardial infarction over an 18-year period. There was a relatively large proportion of women. While the immediate mortality rate was originally high, it dropped slowly over a period of years and then fell rapidly coincident with the use of anticoagulant drugs After the patient has gotten over his acute coronary episode, he is faced with what has been called the postcoronary syndrome (23). The main complaints are tightness and soreness in front of the chest, difficulty in breathing, and weakness or tiredness. It is believed that severe restrictions of physical activity beyond the requirements imposed by limited cardiac reserve afford very little protection to the patient who has survived an acute attack

Not all pain over the precordium is coronary pain. There is skeletal pain, the hyperabduction syndrome, displacement of the costo-chondral cartilage, disorders of the spine, and disorders of the diaphragm and pain from hyperventilation. During the last year it has been pointed out that increased pressure in the pulmonary artery may produce pain which closely mimics the pain seen in angina pectoris or in coronary insufficiency (24). In contrast to anginal pain, this pain is not relieved by nitroglycerine but responds well to aminophylline

In the treatment of myocardial infarcts, the argument for and against anticoagulant therapy has been continued during the past year Russek and co-workers (25) recommend that anticoagulants be employed only in the more serious attacks of coronary infarction This is contrary to the recommendations of the committee for the evaluation of anticoagulants in

acute pericarditis, ventricular aneurysm and acute myocardial infarction. It should not be forgotten that the electrocardiogram may fail to indicate impending cardiac disaster, and that it does not measure the cardiac reserve. In myocardial infarction the electrocardiographic alterations produced by the infarct may clear rapidly and the diagnosis of an early infarct cannot always be excluded because the electrocardiogram is normal It may permit etiologic diagnoses only under special circumstances and then only by inference based upon clinical experience. The value of the electrocardiogram in the detection of heart disease has been described by Dawber and associates (42). The authors selected Lead I of the electrocardiogram as the one which would best fit their requirements. They believed that this method is of value in the detection of heart disease. Graettinger, Packard and Graybiel (43) reviewed the relationships of the axis and amplitudes of the deflection of the bipolar and unipolar leads. By appropriately increasing the sensitivity of the recorder, unipolar limb leads were obtained. The amplitude and areas of deflections were equivalent to those obtained for mensuration of the bipolar leads with respect to the magnitude of the cardiac vector. By reversing the polarity of the connections between patient and recorder, six additional curves of reciprocal form were obtained. When the 12 curves were properly arranged, they represented 12 different views of the electric beat of the heart in the frontal plane. The advantages of such an arrangement are discussed and illustrations are given of some of the advantages for clinical electrocardiography. Langner (44) used the cathode ray oscilloscope to record the electrocardiogram He found significant differences between the records obtained with the cathode ray oscilloscope and the conventional records. The changes of the electrocardiogram in poliomyelitis were described by Manning & Yu, who found a large incidence of abnormal electrocardiograms (45). The most common findings were abnormal T-waves. The changes were greater in adults than in children and in patients with bulbar paralysis.

The choice of precordial leads in the diagnosis of coronary artery disease was discussed by Pomerance and associates. (46)

Studies in intracardiac electrography performed by Levine & Goodale revealed the effect of coronary sinus catheterization on the electrocardiogram (47). Supraventricular premature beats developed during manipulation of the catheter, while ventricular premature beats were recorded with the catheter in the middle cardiac vein Intracavitary potentials of the left ventricle of man were studied by Coelho and co-workers (48) They introduced a catheter with an electrode attached to it through the radial artery into the left ventricle under fluoroscopic control. Auricular potentials were obtained from the catheter in the aorta Ventricular potentials were recorded from normal individuals and from patients with aortic insufficiency, mitral stenosis, and left ventricular hypertrophy. The electrocardiogram obtained from the ascending or descending aorta has the same shape as that recorded from esophageal leads, and its pattern is similar to epicardial but not to

complicated by severe and profound shock. No untoward effects of the drug were noted. Hellerstein and co-workers (35) used methentermine (Wyamine) successfully in the treatment of cardiogenic shock following myocardial infarction.

Cortisone has also been tried in experimental myocardial infarction. Johnson and co-workers (36) believed that cortisone brings about a marked reduction in the size of experimentally produced myocardial infarcts Cortisone did not interfere with the wound healing. In similar experiments Chapman and co-workers (37) produced experimental myocardial infarction in dogs by ligation of the left anterior descending coronary artery and treated the animals with cortisone for 10 days. The authors found atrophy of the adrenal gland following the treatment with cortisone No deleterious effects of cortisone therapy were found as far as the gross or histological appearance of myocardial infarctions were concerned.

Medical aspects of the surgical treatment of coronary artery disease have been described by Beck and associates (38) The article describes the experimental work on animals which demonstrates that oxygenated blood delivered into the venous system of the heart can protect it against occlusion of a major coronary artery. The authors describe the effect of the operation on 28 patients with coronary heart disease. There were 23 recoveries and five deaths. The effect of arterialization of the coronary sinus in dogs on mortality following acute coronary occlusion has been studied by Eckstein and his co-workers (39). The authors are of the opinion that arterialization of the coronary sinus protects the hearts from ventricular fibrillation following coronary artery ligation. In a later paper, Eckstein and his associates (40) come to the conclusion that the beneficial effect of arterialization of the coronary sinus is the result of the establishment of collateral circulaton to the cardiac muscle. Immediately following the operation, retrograde flow through the coronary veins may be observed. Actual backflow from the graft in significant quantity takes place to up one month after the second stage of the operation has been done. Then gradually, all backflow comes from intercoronary channels, and in the dog with normal coronary inflow, none of it is from the graft.

Electrocardiography and Arrhythmias

Rosenbaum has defined the place of the electrocardiogram in cardiac diagnosis (41). He emphasized, that when paroxysmal rapid heart action [illegible]

tance of correlation of the electrocardiogram with the entire clinical picture. He warns against emphasizing minor changes in the electrocardiogram. Persistent elevation of RS-T segment can occur in normal persons and must be differentiated from the elevation of the RS-T segment occurring in

Intrabronchial electrocardiography has been described by Langner & Atkins (72). The authors found that the distribution of potential variations in the lungs of the QRS complex corresponds approximately and qualitatively with the distribution of potential variations recorded from the body surface. They believe that intrabronchial electrocardiography is a useful technique to determine whether the cardiac action currents are distributed to the body surface by preferential pathways or throughout the body as though it were an approximate field.

The effects of posture on atrioventricular conduction are dealt with in a paper by Sherf & Dix (73). In a great number of patients, shortening of the conduction time appeared from the recumbent to the upright positions. In many instances, atrioventricular conduction time became normal The changes of the PR interval are independent of the alterations of the RS-T segment and the T-wave. Sandberg and associates (74) dealt with intermittent and transient bundle-branch-block. They believed that the presence of underlying heart disease, tachycardia, infection, and anemia may impair conduction in the bundle branches. The authors deal in detail with the various aspects of conduction in the bundle branches. The effect of potassium intoxication on the T-waves of normal amplitude was studied by Levine and co-workers (75). The authors demonstrate that certain individuals may show as the earliest or only electrocardiographic evidence of potassium intoxication, "tent-shaped" T-waves of normal amplitude This change is generally correlated with an elevated serum potassium level and in most cases with a simultaneously lowered serum sodium level. The action of several cardiac glycosides on conduction velocity and ventricular excitability in the dog heart was studied by Moe & Mendez (76). Digitoxin, ouabain and other glycosides caused an initial slight increase followed by a decrease of ventricular excitability and depression of atrioventricular and interventricular conduction. It is of interest that the conduction, while depressed in the specialized tissue, was well maintained in the muscle itself. No significant differences between the glycosides were observed.

Caruso and co-workers (77) describe the configuration of electrocardiograms taken by means of direct application of electrodes to the epicardial surface of the heart A fairly good correspondence between the unipolar precordial leads and the direct epicardial leads was found in cases of left ventricular hypertrophy. The same correlation was not so strictly obtained in cases of right ventricular hypertrophy.

Scherlis and associates (78) describe in detail the magnitude, direction, and sense of the vectocardiographic loops on 62 normal children and adults. The vectocardiograms were recorded and photographed simultaneously in the horizontal, sagittal and frontal planes. Also the alterations of the QRS and T loops with respiration are described Burger & Den Boer (79) compare three systems of vectocardiography and the results obtained from different positions of the electrodes A comparative study was done on 115 cases using the systems B_1, R_2, and W_4 A quantitative measure for the corre-

endocardial derivations. Intracavity electrocardiograms from the left ventricle were also obtained by Zimmermann and co-workers (49) and Steinberg *et al.* (50). Right ventricular cavity electrocardiograms were studied by Fowler and associates (51). These authors conclude from their studies that the delayed R wave of the QR pattern in the V leads obtained over the hypertrophied right ventricle, is probably produced by activation of the free wall of the right ventricle. Bellet & Finkelstein (52) described the clinical conditions which are associated with prolongation of the QT interval. They believed that QT segment prolongation together with characteristic ST and T wave changes is an important diagnostic criterion of a diminution in the serum calcium and potassium. The effect of serum potassium changes on the electrocardiogram is further discussed (see 53 to 56).

The significance of the QT interval was discussed by Lepeshkin & Surawicv (57). Sources of error in determination of the beginning of the QRS and the end of the T wave during measurement of the QT derivation are pointed out. The authors believe that the true corrected Q-T duration in hypopotassemia without hypocalcemia is not prolonged, but normal or shortened, corresponding to an early appearance of the second heart sound. The relationship of the QT interval and the corrected QT interval of the electrocardiogram to normal respiratory variations of cycle length was studied by De Lalla & Brown (58) Gittleman and co-workers (59) studied the relation of the electrical systole to autopsy findings obtained in acute myocarditis. Further studies on electrical systole have been carried out (60, 61, 62).

Interpretation of the electrocardiogram in children has remained a difficult and controversial topic. Furman & Halloran studied electrocardiograms employing 12 leads in 52 normal infants in the first two months of life (63). They found that the T-wave has unique characteristics in the first few days of life, but conforms to the hitherto accepted standards of behavior after the end of the second week. The relative right ventricular predominance undergoes marked diminution in the third week of life The electrocardiographic patterns of normal children from birth to five years of age were studied by Gros and co-workers (64). The authors found important variations from those seen in later life, particularly during the first week. They found that the vertical and semivertical electric positions were the most frequently encountered in this age group. QRS duration is shorter in the younger age groups and increases slowly with age. Goodwin measured the electrocardiogram in children from the age of 1 to 15 years (65) The tracings were compared with those obtained from children of similar ages with right ventricular hypertrophy. The author believes that, in certain cases, extreme clockwise rotation may play a part in the production of the pattern seen in right ventricular hypertrophy. Further studies on the electrocardiogram in children have been performed (66 to 70). The most extensive work on electrocardiographic studies in normal infants and children has been published in book form by Ziegler (71).

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spondence of the vectocardiograms according to the three different systems was defined, and the authors found that the first two systems show more correspondence between loops of successive heart beats than the system of the equilateral tetrahedron or system W_4.

A constant deviation of the QRS loop of the vectocardiogram was found in cases of anterior cardiac infarction (80). A similar deviation of the loop away from the site of infarction was seen in cases of posterior infarction. The former deviation was best seen in the horizontal plane, the latter in the frontal plane. An unusual configuration of the vectocardiograms in patients with congenital heart disease associated with definite hypertrophy of the right ventricle were described by Lasser & Grishman (81). The authors believe that the unusual patterns could be caused by the increased thickness and mass of the right ventricle and consequent alteration of the balance of the electromotive forces

The physiologic mechanism of arrhythmias has been extensively studied during the past year. Fox and associates described studies on the mechanism of the arrhythmias in aberrant atrial ventricular conduction (Wolff-Parkinson-White, W.P.W. syndrome) (82). They stressed the frequent occurrence of arrhythmias in the W.P W. syndrome which accounts for palpitation and dizziness; apparently arrhythmias are the most frequent cause of fatalities reported in the literature in patients with this syndrome. It appears that supraventricular arrhythmias are due to lifting of the block of the atrioventricular node and simultaneous oppression of functional activity in the lower portion of the aberrant atrioventricular pathway; ventricular tachycardia is due to the presence of simultaneous block in both the atrioventricular node and the aberrant pathway, and the arrhythmias in general in Wolff-Parkinson-White's syndrome are the result of fluctuations in the level of available vagus substance. Prinzmetal and associates (83) dealt with the mechanism of accelerated conduction (Wolff-Parkinson-White syndrome and related condition). In this monograph the production of W.P W. complexes by mechanical, chemical, and direct electrical stimulation is described and the clinical significance of nodal type of accelerated conduction is discussed. Two experimental types of W.P.W., a nodal and a ventricular type, are distinguished W.P W. aberration depends on the presence of an intact normal conductive system. The authors introduce the term "accelerated conduction" to describe the physiological process which accounts for the premature transmission of the excitation wave from the auricles to part of one ventricle in W.P W. aberration. The term "accelerated conduction syndrome" is reserved to the congenital aberration as described by Wolff, Parkinson and White The term "accelerated conduction beat" is used to describe individual beats in all forms of accelerated conduction whether congenital or acquired. The most important example of the nodal type is the congenital accelerated conduction syndrome. Further studies on W.P.W. as produced by catheterization of the heart have been performed by Kossmann *et al.* (84). The electrokymogram in W.P.W. syndrome has been investigated by Dack *et al.* (85).

The mechanism of auricular flutter has been studied by Prinzmetal and co-workers (86). The authors expanded on this arrhythmia as investigated by direct and sensitive investigative techniques They believed that the circus movement is invalid to explain the production of auricular flutter. Both the contraction and the excitation waves of auricular flutter arise from the ectopic focus and spread outward through the auricles in all available directions simultaneously. No circus movement is present. The course of the contraction in this arrhythmia is similar to that of premature auricular systole and auricular paroxysmal tachycardia. The various electrocardiographic and therapeutic differences between auricular tachycardia and flutter are related to differences in auricular rate and do not indicate a fundamental difference in mechanisms of the two arrhythmias.

The clinical manifestations and the physiological basis of arrhythmias has been stressed in a review by Katz (87) Katz divides arrhythmias into disturbances in impulse initiation and impulse conduction He distinguishes, in the case of impulse conduction, between the phenomena of the normal refractory period and actual depression of the conduction process with abnormal prolongation of the refractory phase. Katz reviews the current work on physiology of arrhythmias, dealing with the work of Sherf and Prinzmetal and with the effect of procaine amide and quinidine. He points out that in complete heart block, convulsions and unconsciousness are often the result of inadequate circulation arising not from slow heart action, but from intermittent paroxysmal ventricular tachycardia. Consequently, sympathomimetic drugs may aggravate the situation. The physiologic effects of increased heart rate are also described. As the heart rate increases, the diastolic volume, and with it the stroke volume, diminishes However, as a result of increased rate, the minute volume will be augmented With further increase in heart rate, cardiac filling decreases and the diastolic and stroke volume decline rapidly leading to a decline in minute volume. De la Chapelle & Rose (88) deal with the clinical aspects of arrhythmia and describe the treatment of paroxysmal superventricular tachycardias, auricular fibrillation, auricular flutter, ventricular tachycardia, complete heart block, and congestive failure In the treatment of cardiac tamponade the authors suggest early aspiration and sometimes rapid administration of intravenous saline The increase in venous pressure thus produced will frequently overcome the resistance to the return of the blood to the right heart.

Lundy & March suggest digitalis in fast auricular fibrillation when the ventricular rate is more than 100 (89). However, the intravenous administration is not warranted The use of quinidine is also discussed Digitalis, in the treatment of paroxysmal auricular tachycardia, has been advocated by Morris (90), who treated 10 cases of paroxysmal auricular tachycardia with intra or intermuscular injections of lanatoside C The administration of the drug resulted in each case in a cessation of the tachycardia and in an abrupt return to normal sinus rhythm Ouabain can cause serious side reactions when it is used in the treatment of this arrhythmia (91). Although parenteral

injection of .5 mg. of ouabain abolished the tachycardia, it produced serious toxic reactions, resulting in complete heart block with Stokes-Adams syndrome. The work of Dick & McCawley (92) in treatment of auricular fibrillation by the intravenous use of antihistamine drugs is of interest. In 12 patients with auricular fibrillation, the antihistamine drugs restored normal sinus rhythm in six individuals; in two it was ineffective, and the desired result was obtained only by giving large doses of quinidine by mouth. In the remaining four the fibrillation persisted despite the administration of both drugs.

The present status of the therapy of the cardiac arrhythmias with quinidine was reviewed by Sokolow (93). The most effective methods for administration of quinidine are discussed. It is stated that with a single dose of quinidine taken orally, the effect is at its peak in 2 to 3 hr , begins to subside in 4 hr., is about half dissipated in 8 hr., and usually has ceased at 24 hr. Therefore, a 2-hr. dosage interval is logical. Five 2-hr. doses have been found to be most effective. If, after five doses, the administration is continued at the same time intervals, metabolic breakdown keeps pace with the additional drug intake, so that the blood concentratoin does not usually rise further. The dosage, therefore, has to be adjusted accordingly.

Sokolow (93) suggests digitalization of all patients with chronic auricular fibrillation before the use of quinidine is attempted. He emphasizes that conversion results in an increase in exercise tolerance and the ability to return to more active life. It is possible that this increase in exercise tolerance is related to an increase in cardiac output (94). As hazards of quinidine therapy, Sokolow mentions idiosyncrasies, such as possible systemic embolism, sudden death, and ventricular arrhythmias. Ventricular tachycardia has occurred in 2 out of 111 patients with auricular fibrillation in whom conversion with quinidine was attempted. Further untoward effects of quinidine are hypotension, conduction defects, and auricular flutter. Sokolow believes that all patients with chronic auricular fibrillation should be given a trial of quinidine, except those with severe conduction defects, subacute bacterial endocarditis, and angina pectoris. The conditions which respond most favorably are auricular fibrillation, persisting two weeks after thyroidectomy, auricular fibrillation in patients with minimal or no enlargement of the heart and no cardiac failure, and finally, chronic auricular fibrillation in an individual with an otherwise normal heart. Sokolow's criteria for the administration of quinidine are supported by the findings of Yount and associates (95), who found that quinidine restored normal sinus rhythm in 86 per cent of patients suffering from arteriosclerotic rheumatic heart disease The duration of fibrillation and severity of the disease did not influence the result of treatment with quinidine. In patients with thyrotoxicosis, [illegible] exceedingly difficult. Further [illegible] by [illegible] was previously mentioned that there seems to be no contraindication to the use

of quinidine in patients who had several attacks of recurrent embolism because of auricular fibrillation. Lackay & Housel (99) found that recurrent attacks of embolism resulting from auricular fibrillation in rheumatic heart disease with mitral stenosis, were terminated following successive administration of anticoagulant therapy.

The action of quinidine on ventricular tachycardia experimentally produced in dogs by narrowing of the anterior coronary artery has been studied by Harris & co-workers (100). Their results show that intravenous quinidine effectively controlled the arrhythmia in 56 to 60 per cent but that toxic reactions appeared in many of them. Morphine sulfate was found to prevent some of the toxic symptoms but did not prevent convulsive movements. Wetherbee (101) described the occurrence of ventricular tachycardia following the administration of quinidine. His findings suggest that this arrhythmia may be a more common result of quinidine administration than it is generally believed. It is of interest that excessive administration of the drug was not necessary to produce ventricular tachycardia.

Since the introduction of procaine amide (Pronestyl) into cardiology, its clinical use has been extensively studied. According to Berry and associates (102) it has been successful in the treatment of these ectopic rhythms. The one condition which the drug was unable to revert to normal rhythm was auricular flutter or auricular fibrillation. In these conditions, quinidine seems to be the method of choice. Berry believes that the oral route is considered to be superior; the present reviewer, however, has found a considerable prolonged fall in arterial pressure following this route. The most serious toxic manifestation is the development of hypotension which follows the rapid intravenous injection of the drug. In supraventricular arrhythmias, McCord & Taguchi found the drug to be effective (103). However, in four patients with auricular flutter, conversion to normal sinus rhythm was not achieved. The use of procaine amide in the treatment of ventricular tachycardia has been investigated (104 to 107). The results in restoring normal rhythm in this arrhythmia have been encouraging.

In contrast to the experience of the present reviewer, Zinn and co-workers (108) found that quinidine and procainamide prevent the occurrence of catheter-induced arrhythmias as long as the irritation produced by the catheter is moderate. The present reviewer believes that the dangers of these drugs are too great to warrant their use in the prevention of catheter induced arrhythmias Further work on the effect of procaine amide has been published (109, 110, 111).

Cardiac Failure: Congestive Failure

Several reviews have been published dealing with the general problem of congestive failure (112 to 115). Stead (116) discusses the various types of edema in congestive failure; (*a*) edema caused by a redistribution of fluid normally present in the body, and (*b*) that caused by a gain in weight indicating an abnormal accumulation of salt and water. The first type is seen

in patients who develop a left ventricular infarct; the second type occurs in congestive heart failure. He dwells on his ideas of the role of the kidney and the retention of sodium and water. Sodium retention is the result of low filtration rate in the presence of reasonably well functioning tubules. The problem of primary water retention in congestive failure is discussed. This topic is also dealt with by Miller (117). A discussion of general physiological problems of cardiac failure has been published (118, 119, 120). Bing & Taeschler (120) discuss the relationship between cardiac failure and heart muscle. Significant differences in myocardial metabolism of glucose were found *in vivo* in normal and failing hearts The interruption of the link between aerobic energy or the energy from breakdown of glucose and mechanical work seems to be one of the essential findings in cardiac failure. In myocardial failure, the carbohydrate consumption by the heart is increased, but the heart has lost some of its ability to convert aerobic energy derived from carbohydrates into useful work.

The problem of cardiac edema was dealt with in detail by Peters (121). In this review, the author discusses factors responsible for the reabsorption of water and salt. It is believed that the logic of the conventional theory of the formation of cardiac edema, with its sequence based on Starling's principles, cannot be lightly set aside. A large amount of literature has accumulated on electrolyte changes occurring in congestive failure. Stok and associates (122) made observations to ascertain the electrolyte abnormalities that might accompany congestive failure when treated with digitalis, low sodium chloride, and the frequent administration of mercurial diuretics. They record three responses in electrolyte pattern: (*a*) minimal electrolyte abnormalities; (*b*) hypochloremic alkalosis, which was because of the fact that the mercurials produced a relatively greater excretion of chloride than of sodium, and (*c*) depletion of both chloride and sodium. The latter results from the fact that the urinary excretion of both electrolytes is in excess of the water loss. The authors performed muscle biopsies which failed to show significant changes in intracellular cation concentrations. In contrast to the previous authors, Squires and associates (123) conclude that abnormalities of intracellular fluid exist in congestive failure. They calculated the changes in the phases of body fluids following mercurial diuretics and found that a definite portion of the water loss came from the intracellular phase. This intracellular phase shares in the abnormalities of the body fluids of congestive heart failure.

Related to these problems of electrolyte shift between intracellular and extracellular fluids is the work of Mokotoff *et al.* (124) The authors state that the answers as to changes in intracellular electrolyte composition in heart failure depend on whether or not one uses the corrected chloride space or the inulin space as reference standards for extracellular water. Studies performed by Iseri *et al* showed that, on analysis of cardiac and skeletal muscle, potassium concentrations below the control values occurred (125). However, there was no significant change in the content of water,

sodium, chloride, magnesium, or phosphorus in either cardiac or skeletal muscle. Because of the potassium loss, the estimated intracellular concentration of total base was reduced.

Further studies on the distribution of body fluids in congestive heart failure were performed by Prentice and associates (126). These authors studied blood volume with red cells labeled with P^{32}. Less than half of the patients studied with congestive failure had normal blood volume, total red cell volume, and plasma volume. The majority, however, had either elevated blood volume, total red cell volume, or plasma volume. It was found that serum sodium concentration did not change markedly during heart failure but total body sodium rose to a marked degree.

Changes in the sodium excretion in sweat and by the gastrointestinal tract in congestive failure were investigated by a series of workers. Reynolds (127) found that the mean concentration of sodium in sweat of one group of congestive failure patients was significantly higher than that of the controls, that mercuhydrin did not affect sweat sodium concentration, and that in addition to the adrenal cortex, there may be numerous nonendocrine factors that affect sweat electrolyte composition. On the other hand, it has been shown with the use of cation-exchange resin that the colon of the edematous patient retains sodium to a greater degree than the colon of the normal subject. It is believed that accumulation of edema in congestive failure and cirrhosis of the liver is at least partially mediated through a disturbance in the hormonal control of sodium excretion (128).

An interesting report on the equilibrium time of distribution of long-life radiochloride and radiosodium in man with and without chronic congestive heart failure, has been published by Burch and associates (129). The authors measured the time at which the rate of disappearance from the serum of an intravenously administered Cl^{36} becomes constant and measured the time at which the serum concentration of intravenously administered Cl^{36} reaches a fairly constant value and values of space calculated by the dilution technique become constant. They believe that equilibrium of distributions for Cl^{36} in man with and without congestive heart failure occurs after 24 hr. Similar times were observed for Na^{22}. The dangers of salt depletion in heart failure were stressed by Tapley (130). The mental symptoms that occur with salt depletion are also mentioned.

The role of the nervous system in relation to congestive failure has been investigated by a series of authors. Fejfar & Brod (131) believe that the failing heart activates the sympathetic system in the same manner as do other circulatory emergency conditions. This is responsible for the vasoconstriction and the increase in peripheral resistance. Redistribution of blood supply to various organs, and diminished capacity of the arteriolar bed and an active rise in venous tone can also be attributed to these neurogenic mechanisms Halmagyi and associates (132) believe that venous constriction in heart failure is mediated by the sympathetic nervous system and controlled by higher brain centers. The venous hypertension in failure

is the combination of a mechanical factor (high blood volume, back pressure), and a functional factor produced through neurogenic mechanisms. The connection between pulmonary edema, heart failure, and the role of neurologic stimuli has been investigated by Paine and co-workers (133). It is believed that pulmonary edema primarily results from a cardiogenic mechanism.

The influence of changes in environmental atmospheric temperatures and relative humidity on patients with congestive heart failure were observed by Berenson & Burch (134). Their study was concerned with the physiologic reactions of subjects with chronic congestive heart failure and with those of subjects without cardiac disease upon exposure to a hot and humid environment. The hot and humid surroundings precipitated acute attacks of left ventricular failure. Subjects with advanced cardiac disease were less able to combat the stress of environmental heat than were the subjects without cardiac disease.

Higginson and associates (135) observed a form of heart disease in South African Bantu which they believed to be based on chronic malnutrition. There was cardiac dilatation and hypertrophy and some fibrous scarring. The heart in amyloidosis was discussed by Williams (136). The cardiac complications of hemochromatosis are discussed by Bothwell and co-workers (137). A case of hemochromatosis is presented in which heart failure, skin pigmentation, amenorrhea, and enlargement of the liver were present. Studies with radioactive iron absorption indicate a large retention of ferrous sulfate in the body. It is apparent that heart failure in hemochromatosis was related to the rate at which iron is laid down in cardiac muscle rather than to the absolute quantity deposited.

Cardiac catheterization was used in order to investigate the circulatory changes leading to cor pulmonale in metastatic carcinoma of the lung (137). The findings in these patients include arterial oxygen desaturation, hypertension of the pulmonary artery, and right ventricular failure. The author relates the pulmonary hypertension to invasion of the arteries of the lung by cancer cells. Feltman and associates (138) described cardiac failure secondary to ineffective bellows action of the chest cage. Two cases are presented which represent examples of cardiac failure secondary to an ineffective bellows action of the chest cage, without significant intrinsic pulmonary disease.

Capillary permeability in congestive failure was studied by Rovelli (139). An abnormal capillary permeability was observed in patients with congestive failure. Selkurt (139a) summarized peripheral mechanisms in congestive heart failure. The author inter-relates the factors concerned in congestive heart failure. He believes that certain aspects of backward and forward failure complement each other, that is, the elevated venous pressure favors the movement of fluid and salt into the interstitial spaces. This results in reduction of blood volume which contributes to the reduced cardiac output, favors salt and water retention by the kidney, and produces hypervolemia. The response of the peripheral venous pressure to exercise in congestive

heart failure was investigated by Albert & Eichna (140). It was found that both the resting venous pressure and the rise in venous pressure during exercise increased with the severity of congestive failure. They believe that the measurement of venous pressure during exercise is a sensitive index of milder degrees of congestive heart failure. Loring (141) described 87 cases of thrombosis of the veins of the upper extremity as a complication of cardiac failure. He found that the subclavian vein is most frequently occluded Rheumatic heart disease is the most common cause, and hypertensive cardiovascular disease is second. Weyrauch and Rosenberg (142) described a case of heart failure resulting from estrogen therapy for prostatic carcinoma.

The effect of cation exchange resins in cardiac failure has been studied by Wood and associates (143). They did not observe any toxic effects in 50 subjects treated with cation-exchange resins No hypokalemia was encountered when the ammonium-potassium cation resin was used. The chief hazards are the low salt syndrome and azotemia. Impaired renal function is the outstanding contraindication to the use of the cation-exchange resins. Definite improvement was observed in several patients who had responded poorly to conventional methods of treatment, including rigid dietary sodium restriction (144). The electrolyte exchange during initial periods of resin therapy was studied by Elkinton and associates (145). The authors discussed the theory of action of cation-exchange resins. They found an increased fecal excretion of sodium and potassium but the fecal increase of sodium did not greatly exceed the dietary intake of the ion. They report excellent results in patients who were previously refractory to treatment and believe that the exchange resins are a useful adjunct in treatment of refractory cases and are capable of potentiating the action on the kidneys of mercurial diuretics. It is believed that a combination of anion and cation exchange resins increases the sodium removing capacity of the resins by almost one-third (146). The toxic effects of ammonium-potassium carboxylic resins was further discussed (147). Hypocalcemia and hypokalemia were the most common toxic effects and limit the practical usefulness of this resin. Gastrointestinal symptoms and increase in digitalis toxicity were also seen. The initial daily dose of resin was 60 gm. divided into three equal parts taken after meals Subsequent dosage varied with the response. Gilchrist (148) found excellent results of resin therapy combined with mercurial diuretics

Pollock & Gillespie (149) found that mercaptomerin (Thiomerin) can be easily self-administered. A case of agranulocytosis in a patient treated with mercurial diuretics was described by Silverman & Worthen (150). The electrolyte and water loss in patients receiving mercurial diuretics was investigated (151). It was found that the loss of potassium was appreciable following injection of meralluride to patients who almost completely retained their dietary sodium The fluid loss by mercurial diuresis was isotonic with body fluids. The systemic sensitivity to various mercurial diuretics

was discussed by Robbins (152). The author describes one case of congestive failure who developed hypersensitivity to mercurial diuretics The use of combined treatment of mercurial diuretics with aminophylline in patients refractory to mercurial diuretics was described by Vogl & Esserman (153). The regimen consists of the intermittent use of mercurial injections concomitant with multiple daily aminophylline injections.

Thromboembolic phenomena associated with rapid diuresis in the treatment of congestive heart failure has been described by Marvel & Shullenberger (154). During the period of diuresis there was definite hemoconcentration and an increase in blood viscosity in all patients. Prothrombin values tended to increase. The use of anticoagulants during the dehydration period is recommended. A practical method for the bio-assay of diuretic agents in patients with congestive failure is suggested by Greiner and associates (155). The procedure is carried out in ambulatory patients and the period of time elapsed before the patient regains weight after initial injection of the agent is ascertained. This procedure is repeated with varying doses of several preparations.

Congenital Heart Disease

A series of reviews have been published on this subject within recent years. The *American Journal of Medicine* has published a symposium on congenital heart disease containing papers on a classification and introduction to congenital heart disease (156), on cardiac catheterization in the study of congenital anomalies (157), on patent ductus arteriosus (158), on pulmonic stenosis (159), on tetralogy of Fallot (160), and on angiocardiography (161). A diagnostic outline has been given by Bing in which clinical and physiologic findings are correlated (162). Soulie and co-workers (164) state that angiocardiography is of great value in the differentiation of infundibular and valvular pulmonic stenosis and in establishing the exact location of coarctation of the aorta They believe that selective angiocardiography is of great value in the diagnostic workup, but that it is unlikely to replace standard angiocardiography. Nevertheless, it is apparent from their results that selective angiocardiography (the outline of certain selected portions of the heart and the great vessels by means of injection of contrast material into a catheter) has great diagnostic possibilities. Further aspects of angiocardiography in congenital heart disease have been discussed (163, 165, 166). Diagnostic methods and procedures in congenital heart disease have also been described by Grosse-Brockhoff *et al.* (167).

Reviews dealing with electrocardiographic changes in congenital heart disease have been published by Rogers (168). The author is of the opinion that routine electrocardiographic studies in infants with congenital cardiac disease would probably reveal more frequent evidence of disturbances of cardiac rhythm and conduction. In a very interesting paper by Soulie and co-workers (169), the electrocardiographic changes during cardiac surgery are discussed. The authors believe that electrocardiographic tracings during

surgery are of great importance in rapid and correct interpretation of arrhythmias occurring during these procedures. Lequime & Charlier (170) have published a monograph on clinical and physiopathologic findings in congenital malformations of the heart. In this volume the authors discussed modern methods in the study of congenital heart disease with special reference to the operable malformations. Their volume represents a thorough and complete review of the methods used and of the findings obtained.

The physiological findings in congenital heart disease have been summarized by Bing (171). The blood volume in patients with congenital cyanotic heart disease has been measured by Scott and co-workers (172). Both the dye, T1824, and radioactive phosphorus were used Diminished plasma volume, increased red cell and whole blood volumes were found in cyanotic individuals Following operation for pulmonic stenosis, the red cell volume decreased, the plasma volume increased, and the whole blood volume, although somewhat reduced, remained moderately elevated.

It has been known for a number of years that many congenital malformations of the heart produce profound disturbances in the pulmonary circulation. Pulmonary hypertension has been described in patients suffering from auricular and ventricular defects, Eisenmenger's disease, transposition of the great vessels, and in some individuals with patent ductus arteriosus. Edwards and co-workers (173) have continued their studies on pulmonary vascular pathology in congenital heart disease. The problem of pulmonic hypertension was also discussed by Adams (174) and Grosse-Brockhoff and associates (175)

A method has been devised from data obtained by cardiac catheterization to calculate the elasticity resistance as well as the peripheral resistance for both systemic and pulmonary circulations in patients with congenital heart disease (176). The figures give a quantitative expression of differences between the systemic and pulmonary circulations The relation between the elasticity resistance and the occurrence of visible pulsations in the pulmonary arteries on fluoroscopy has been examined. It has been shown that visible pulsations are probably related to the pulse volume or stored portion of the stroke volume in conditions with either increased pulmonary flow or high pulmonary arterial pressure The authors believe that the regulatory mechanism of the systemic circulation in congenital heart disease is predominant and that such regulation as exists in the pulmonary circulation, is subordinate to the needs of the systemic circulation.

Hematologic changes in patients with congenital heart disease who have been subjected to operations designed to improve the circulation to the lung have been investigated by Brinton (177) The author believes that each in-

hemoglobin although the stimulus to erythropoiesis will continue and a greater number of cells than that originally required will be produced The

same author studied 60 postoperative cases and found that there was a lessening of the macrocytosis in patients whose polycythemia was only moderate and an increase of cell size in those patients with microcytosis whose polycythemia was originally more severe. Hartmann found a high incidence of hemorrhagic diathesis in cyanotic patients with congenital heart disease. (178) There was impairment of clot retraction due to thrombocytopénia and low fibrinogen. Consequently the use of anticoagulant drugs in the treatment of thrombosis in cyanotic congenital heart disease may be dangerous.

Studies on the tetralogy of Fallot have indicated that in 43 of the 48 cases studied, stenosis existed in the infundibulum, either as the only site of obstruction to pulmonary blood flow or coupled with obstruction at the pulmonary valve (179). Significant obstruction at the level of the pulmonary valve occurred in 29 of the 48 cases. This obstruction was either restricted to the pulmonary valve or associated with stenosis of the infundibulum. Three cases showed atresia of the pulmonary trunk. In similar studies, Brock (159) has found that infundibular stenosis is not a long tubular stenosis of the right ventricular outflow tract, but that the actual stenosis occurs at one level within the outflow tract and is linear or diaphragmatic. Physiologic studies on patients with pulmonic stenosis in whom valvulotomy was carried out have been published [Soulie *et al.* (180)]. In this report, nine postoperative cases were studied. Little change in heart volume or electrocardiography occurred following operation There was first a rapid decline in the ventricular hypertension which became less as time progressed. There was only a slight rise in pulmonary artery pressure. In most instances, the pulmonary blood flow remained slightly below normal. There was a reduction in the intracardiac shunt but the over-all direction of the shunt from right to left persisted. The authors believe that the variability results from a slow physiologic response to operation. Furthermore, some of the anatomic features which compose the congenital lesions cannot be completely corrected. The electrocardiogram in the tetralogy of Fallot was studied by Woods (181). There were no striking changes in the electrocardiogram taken before and after operation except for coronary T-wave changes in cases in which the direct ventricular operative approach was used

Transposition of the great vessels which, so far, has resisted successful surgical treatment, has been discussed by various authors. Abrams and coworkers (182) described as significant diagnostic signs enlarged heart, increased vascular shadow and narrowing of the superior mediastinum A case of complete transposition of the great vessels with atrial and ventricular septal defect, patent ductus arteriosus, and coarctation of the aorta was described by Nichol and Segal (183). The patient lived 29 years and was in congestive failure only during the last 3 years. The combined presence of a patent ductus and coarctation of the aorta resulted in an appreciable difference in the degree of cyanosis of the upper and lower extremities The case is of particular interest since it illustrates that patients with this malformation, who usually die at an early age, can live for longer periods of time, pro-

vided sufficient exchange between the pulmonary and systemic circulations is possible. Angiocardiographic findings in transposition of the great vessels have been discussed by Castellanos and co-workers (184). The authors believe that angiocardiography is the best diagnostic procedure for the recognition of this malformation. The diagnostic features of transposition of the great vessels are also reviewed by Astley & Parsons (185).

The circulation in transposition of the aorta with levoposition of the pulmonary artery (Taussig-Bing syndrome) was discussed by Martin & Lewis (186), who conclude that this syndrome can be separated from transposition of the great vessels with ventricular septal defect only by angiocardiography and then only in favorable circumstances. It is the reviewer's opinion, however, that catheterization together with the clinical signs is sufficient to arrive at a correct diagnosis. This is in line with the observations of Falholt & Pederson (187) who diagnosed a patient with this malformation by means of clinical and catheterization findings alone. Ziegler (188) has published the diagnostic criteria for patent ductus arteriosus in infants Apparently the diagnosis of uncomplicated patent ductus arteriosus can be made clinically at any age. Ziegler believes that uncomplicated patent ductus arteriosus is frequently a serious defect in infancy and that surgical interference in this lower age group can be safely and successfully performed. He lists the principal indications for operation for patent ductus arteriosus in infants Infants under one year with patent ductus arteriosus usually have only a systolic murmur The main roentgenographic patterns of patent ductus arteriosus in infants are left ventricular and left auricular enlargement, increased pulmonary vascularity, and increased amplitude of pulsations of the pulmonary artery, the aorta, and left ventricle The hemodynamic changes in patent ductus arteriosus were discussed by Voci, Touche & Joly (189) The authors were able to catheterize the ductus in about half of their patients In one patient who showed preoperatively an elevation of the pulmonary artery pressure, the pressure returned to normal following surgical intervention It is believed that pulmonary insufficiency is a frequent complication of ductus arteriosus and that mixing of blood in the pulmonary artery is usually not complete Out of 10 patients, four showed normal pulmonary artery pressure whereas in six others pulmonary hypertension was present The peripheral arterial oxygen saturation was normal in half of the patients and slightly decreased in the remainder. The shunt through the patent ductus represented from 21 to 64 per cent of the total left ventricular outflow The association of a large patent ductus approximating the size of the aorta, pulmonary hypertension, absence of a continuous murmur, and cardiac enlargement was described by Dammann & Sell (190).

There appears to be little doubt that the peripheral hypoxemia in Eisenmenger's complex is attributable solely to the veno-arterial shunt from the right ventricle to the overriding aorta. This was first postulated by the reviewer, and has been confirmed by Goldberg and associates (191). Recent attempts at surgical correction of Eisenmenger's disease by the creation of a

pulmonic stenosis suggested by Civin & Edwards (192) are discussed, and the conclusion is reached that this procedure would be highly unsatisfactory.

The cause of hypertension in coarctation of the aorta is still the subject of debate. Gupta & Wiggers (193) believe from experimental studies that the hypertension in the aorta above a coarctation is not solely a result of increased vascular resistance, as has been commonly inferred. Equally important are the reduced capacity and distensibility of the aortic compression chamber and the physiologic reactions of the left ventricle whereby its systolic discharge is increased. There is also evidence for compensatory increase in flow through the coronary vessels. The authors believe that hypertension of aortic coarctation as resulting from renal factors is difficult to reconcile with dynamic loss. On the other hand, Scott & Bahnson (194) were able to produce coarctation in the dog and to reduce the hypertension existing in the upper portion of the body by transplanting the remaining kidney from the lower to the upper part of the body.

The clinical recognition of pulmonic stenosis with closed ventricular septum has become of paramount importance because of the surgical treatment of this malformation. Abrahams & Wood (195) found that in their series there were 37 cases of simple pulmonary valvular stenosis and eight of infundibular stenosis. The authors believe that an accurate diagnosis is nearly always possible and that infundibular stenosis may clinically be distinguished from valvular stenosis by the low position of the thrill, occasionally by the absence of a parasternal lift, by the absence of dilatation of the pulmonary artery, and by means of cardiac catheterization. The malformation has also been described by Coelho and co-workers (196).

The roentgen aspects of pulmonary arteriovenous fistula have been discussed by Seaman & Goldman (197). The authors believe that conventional roentgenograms should be supplemented by laminagrams. Angiography is of great value in demonstrating multiple lesions which may not be discovered by other techniques. Roentgenologic findings in tricuspid atresia have been discussed by Wittenborg *et al* (198). The clinical and catheterization data in Ebstein's anomaly were described by Van Lingen *et al.* (199). Cardiac catheterization showed a higher systolic pressure in the distal part of the right ventricle than was found in its proximal portion. There was evidence for an over-all right to left auricular shunt. The clinical picture was described as that of a delayed onset of cyanosis, systolic and mid-diastolic murmurs, a single second heart sound at the base of the heart, and right bundle branch block. Radiological studies showed a markedly enlarged right ventricle, sufficiently characteristic to be of diagnostic value. Aneurysm of the coronary arteries and of the sinus of Valsalva were discussed (200, 201).

Mitral Stenosis

The rapid progress in the surgery of mitral stenosis has stimulated the interest of physicians and physiologists alike. There is little doubt that operation on the mitral valve is beneficial. Nevertheless, not all the questions con-

cerning the selection of patients for operation have as yet been answered. Problems of this nature were discussed in a series of papers (202, 203, 204). Most of these reports deal with the anatomy, the life cycle, and the clinical classifications of mitral disease. Harken and co-workers (203) describe in detail the anatomy of the mitral valve and state that there are considerable variations in the leaflet arrangement. Patients with mitral stenosis have a clear-cut history of a previous rheumatic infection in only about one-hlaf of the cases and it takes considerable time to produce the symptoms of mitral stenosis. Heart failure accounts for 44 per cent of the deaths, and in an additional 33 per cent, death is from acute events, such as embolic phenomena. Pulmonary infarction is fatal in 11 per cent of patients with mitral stenosis. Harken believes that the surgeon should be primarily concerned with patients who have increasing pulmonary difficulties that can be explained largely on a mechanical basis as a result of elevated pressure in the pulmonary capillaries. The author divides patients with mitral stenosis into four groups, benign, handicapped, progressive, and terminal. He lists as relative contraindications to operation, active rheumatic carditis, mitral regurgitation, and severe aortic valvular disease. Andrus (204) lists as contraindication for operation, acute rheumatic carditis, bacterial endocarditis, intractable right heart failure, frequent or recent embolism, mitral insufficiency, and lesions of other valves, particularly aortic stenosis. Janton and associates (202) select patients for commissurotomy by dividing them into seven categories according to history, age, valvular defect or defects, cardiac size, electrocardiographic findings, functional capacity, and complicating factors such as rheumatic activity, arrhythmias, and embolic episodes They divide the clinical stages of mitral stenosis into an asymptomatic, statically incapacitating, progressively incapacitating, terminally incapacitating, and irretrievable stage. It is believed that surgery in the irretrievable stage should be avoided and that surgery should be done in the incapacitating stage to a greater extent.

Changes in the pulmonary circulation in mitral stenosis have been discussed by Lukas & Dotter (205). Their findings agree with those published in previous papers on this subject The hydrostatic pressure in the pulmonary capillaries was frequently equal to the plasma colloid osmotic pressure and even exceeded it during brief periods of exercise without development of frank pulmonary edema. Electrocardiographic and auscultatory changes following mitral valvuloplasty are discussed by Spiegl and co-workers (206). The auscultatory changes consisted primarily in a decrease in apical mitral diastolic murmur, the development of an apical systolic murmur of grade III intensity was generally indicative of a poor postoperative result. An interesting discussion of the Austin Flint murmur was published by Wade and co-workers (207). The authors describe a patient with typical Austin-Flint murmur in whom radiologic and hemodynamic studies did not reveal any evidence of mitral stenosis Their data do not suggest a rise in left auricular pressure as cause of the murmur, nor was there any obvious dilatation of

the left ventricle, indicating that the Austin-Flint murmur was a true relative murmur existing without organic mitral disease and without elevation in left auricular or pulmonary capillary pressure.

It may be noted that the problem of recognition of mitral insufficiency by pressure tracings was examined by Winn *et al.* (208). These authors studied the left auricular pressure pulse in patients with and without mitral valve disease during thoracotomy. They found that in patients with evidence of mitral incompetence, including some in whom this developed after valvulotomy, no significant difference in the form of the left auricular pressure pulse was found from those considered to have mitral stenosis alone. It is apparent from these studies that in the presence of mitral stenosis, mitral regurgitation does not produce any qualitative changes in the form of the left auricular pressure tracings. This finding is in agreement with that obtained by Calazel and co-workers (209). The intrathoracic blood volume in mitral stenosis and left ventricular failure has been studied by Kopelman & Lee (210). The authors, using the dye dilution curve for the estimation of mean intrathoracic blood volume, found that in mitral stenosis the intrathoracic blood volume was only slightly increased.

The physiologic pattern in mitral valvular disease is conditioned by both the disease of the valve and by changes in the pulmonary blood vessels The effects of work on the pulmonary circulation in mitral stenosis were studied by Eliasch and co-workers (211). In several of their patients the pulmonary capillary pressure rose promptly with exercise and remained elevated. It is believed that this was only partially because of a corresponding rise of the left auricular pressure. The authors are not certain about the factors determining changes in pulmonary capillary pressure during exercise and emphasize the necessity to maintain effort for a period longer than 4 to 5 min. They make the logical statement, that in certain patients with mitral stenosis where pulmonary vascular changes are extreme, the limited ability of the cardiac output to rise on effort may not be directly dependent on the orifice of the mitral valve, but rather on the degree of pulmonary arteriolar narrowing.

A correlation between clinical and physiologic findings in mitral stenosis has been attempted by Ellis and co-workers (212). The authors relate the degree of clinical disability to cardiac output, pulmonary arterial pressure, and pulmonary resistance. They believe that good correlation exists between clinical disability and pulmonary artery pressure and pulmonary resistance. They discussed the possible mechanism of pulmonary edema occuring in mitral stenosis and believe that acute failure of the left auricle may be responsible for the initiation of the attack, but that the degree of myocardial damage and insufficiency in relation to the degree of mitral obstruction may also be of importance. Studies on individual factors regulating the pressure relationship in mitral stenosis have been continued (213) Of interest to the general problem of heart failure are the results obained by Werko and his associates (214) on renal function in mitral stenosis. These workers found a

good correlation between the renal plamsa flow and the filtration fraction on the one hand, and the pressure in the pulmonary artery on the other. It was of particular interest that the right auricular pressure was not increased at a time when the changes in the renal circulation were already significant. It appears that in mitral valvular disease, the blood flow is deviated from the kidneys as a result of changes within the kidneys themselves, even before any signs of heart failure have appeared.

Hypertension

The quest for therapy of hypertension has continued, although there has been some slackening in the efforts to define the various causes underlying this disorder. For this reason, the following section will be primarily devoted to work dealing with aspects of therapy of hypertension

Werko and associates (215) studied the clinical and hemodynamic effects of intravenous hexamethonium bromide in hypertensive patients The largest intravenous dose of hexamethonium bromide which could be given safely was not more than .2 mg./kg. body weight A fall in pulmonary capillary and pulmonary artery pressure as well as a decrease in cardio-pulmonary blood volume was observed There was usually a decline in cardiac output Apparently these changes resulted from pooling of blood in the systemic circuit Campbell and associates (216) reported on treatment of hypertension by oral methonium compounds They attempted to establish whether or not control of hypertension and relief of symptoms can be accomplished by oral administration. They were able to alleviate or to remove symptoms, and to effect the disappearance or marked regression of physical signs Smirk believed that two or three subcutaneous injections daily of pentamethonium or hexamethonium haloids were sufficient in reducing high arterial pressure (217) With continuous subcutaneous injections of these compounds, the arterial pressure remained within the selected range for a period of up to 10 days. Apparently, continuous infusion was of particular value in the treatment of hypertensive crises. Restall & Smirk (218) found that hexamethonium bromide alters the relationship between cardiac output and peripheral resistance in such a way that for any given cardiac output the peripheral resistance is less than it would be in the absence of the drug The postural hypotension following the injection of the drug appears to be the result of a change in the capacity of vessel walls of dependent parts to contract and thereby resist gravity pressure dilatation. In comparing the subcutaneous administration of methonium salts to their oral ingestion, Kilpatrick & Smirk (219) found that the effects of oral administration continued longer but were less predictable. Symptoms of intolerance developed in a larger proportion of patients when the effective doses were given by mouth Murphy (220), using hexamethonium bromide, both orally and subcutaneously, found that although tolerance to hexamethonium may develop, some patients became more sensitive to the drug during the treatment. Fullerton & Milne (221) studied the effects of hexamethonium compounds on three

the left ventricle, indicating that the Austin-Flint murmur was a true relative murmur existing without organic mitral disease and without elevation in left auricular or pulmonary capillary pressure.

It may be noted that the problem of recognition of mitral insufficiency by pressure tracings was examined by Winn *et al.* (208). These authors studied the left auricular pressure pulse in patients with and without mitral valve disease during thoracotomy. They found that in patients with evidence of mitral incompetence, including some in whom this developed after valvulotomy, *no significant difference in the form of the left auricular pressure* pulse was found from those considered to have mitral stenosis alone. It is apparent from these studies that in the presence of mitral stenosis, mitral regurgitation does not produce any qualitative changes in the form of the left auricular pressure tracings. This finding is in agreement with that obtained by Calazel and co-workers (209). The intrathoracic blood volume in mitral stenosis and left ventricular failure has been studied by Kopelman & Lee (210). The authors, using the dye dilution curve for the estimation of mean intrathoracic blood volume, found that in mitral stenosis the intrathoracic blood volume was only slightly increased.

The physiologic pattern in mitral valvular disease is conditioned by both the disease of the valve and by changes in the pulmonary blood vessels The effects of work on the pulmonary circulation in mitral stenosis were studied by Eliasch and co-workers (211). In several of their patients the pulmonary capillary pressure rose promptly with exercise and remained elevated. It is believed that this was only partially because of a corresponding rise of the left auricular pressure. The authors are not certain about the factors determining changes in pulmonary capillary pressure during exercise and emphasize the necessity to maintain effort for a period longer than 4 to 5 min They make the logical statement, that in certain patients with mitral stenosis where pulmonary vascular changes are extreme, the limited ability of the cardiac output to rise on effort may not be directly dependent on the orifice of the mitral valve, but rather on the degree of pulmonary arteriolar narrowing

A correlation between clinical and physiologic findings in mitral stenosis has been attempted by Ellis and co-workers (212). The authors relate the degree of clinical disability to cardiac output, pulmonary arterial pressure, and pulmonary resistance. They believe that good correlation exists between clinical disability and pulmonary artery pressure and pulmonary resistance. They discussed the possible mechanism of pulmonary edema occuring in mitral stenosis and believe that acute failure of the left auricle may be responsible for the initiation of the attack, but that the degree of myocardial damage and insufficiency in relation to the degree of mitral obstruction may also be of importance. Studies on individual factors regulating the pressure relationship in mitral stenosis have been continued (213) Of interest to the general problem of heart failure are the results obained by Werko and his associates (214) on renal function in mitral stenosis. These workers found a

trum viride and tetraethylammonium chloride in hypertension, and observed a similar arterial pressure fall to each drug when they were given on the same day It appeared that vasodilatation produced by veratrum viride is not specific in terms of the various mechanisms interrelated in the maintenance of the elevated blood pressure, but depends on the degree of severity of peripheral resistance which is present. Kauntze & Trounce (229) observed that veriloid by mouth lowers the arterial pressure in about two-thirds of hypertensive patients. However, in half of these the hypertensive level closely approached the toxic level. This only left some 20 to 30 per cent in whom the drug was a staisfactory hypotensive agent. Phenobarbital was the most useful agent in diminishing toxic symptoms. Wilkins (230) agrees that the therapeutic margin of these drugs is highly critical, since the difference between nonhypotensives and excessive hypotensive doses is small, and the range between symptom-free and nauseating hypotensive dose is narrow.

The action of dihydrogenated derivative of three ergot alkaloids, ergocornine, ergocristine and ergocryptine (Hydergine) on cerebral blood flow was studied by Taeschler, Cerletti & Rothlin (231). The drug decreased the cerebral vascular tone in the cat. Gibbs (232) found that subjects with minimal peripheral arteriosclerosis and good renal function are most liable to show a satisfactory response to Hydergine. (232) Subjects with malignant hypertension and good renal function showed the best response The side effects were few and consisted in mild drowsiness, nasal congestion, and slowing of the heart rate. Dupuy, Signorelli & Attyah (233) concluded that dihydrogenated ergot alkaolids are capable of lowering the blood pressure only when given in sufficiently large doses. However, they believe that the practical application of these drugs is limited because of the extreme low incidence of hypotension and its short duration.

Perera (234) has confirmed the observation of others that the addition or substraction of dietary salt has a small but consistent effect on the blood pressure of uncomplicated hypertensives, but is without effect in normotensives Excessive salt intake does not influence the arterial tension in the hypertensive with adrenalcortical insufficiency unless small daily injections of desoxycorticosterone are administered These observations suggest that the sodium ion is related to arterial pressure regulation, that the hypertensive handles salt or its restriction in a manner different from normal, and that an intact adrenal is necessary for this action The response of the kidney in reducing filtration rate as the blood sodium intake decreases is of interest. With careful sodium balance studies, restriction of dietary sodium caused statistically significant reduction in the average arterial pressure in patients with uncomplicated hypertension (235) Weight losses and large variations in the intakes of protein and water were without significant effect on the pressure It is possible that the low-sodium diet exerted its beneficial effect by causing an increase in cellular hydration. Brandt and associates (236) have shown that substitution of hypertonic solutions of sodium chloride for drinking water will cause arterial hypertension in the rat. This hypertension

groups of patients. The first group had marked impairment of renal function; the second had fixed hypertension, all showing a similar psychological behavior pattern in that they were extremely active. The third group showed a marked fall in arterial pressure soon after hospital admission although they were not confined to bed. In the first group the hexamethonium preparations were useful therapeutic aids. In the second group the use of hexamethonium by mouth appeared to be of no value. Parenterally, they were of limited value in this group. In the third group the effective treatment was particularly difficult to evaluate. Apparently, hexamethonium bromide is more powerful than pentamethonium bromide (222).

In this country, Freis and associates (223) found that the toxic reactions to the drug are due entirely to blockade of the autonomic ganglia. Toxic symptoms consisted in postural hypotension, constipation, paralytic ileus, and urinary retention. The authors found cholinergic agents to be most useful in restoring bowel motility. The effective dose was determined by intravenous infusion (1 mg of the ion per min. until a total of 10 mg had been administered). Phenylephrine (Neosynephrine) was used to restore arterial pressure if it had fallen too low. In a series of patients, the hexamethonium compound was used together with 1-hydrazinophthalazine (Apresoline). The authors agreed with Smirk that oral administration is less effective than the parenteral administration Schroeder (224) also recommended combined treatment of hexamethonium with hydrazinophthalazine. It is believed that the toxic effects of hydrazinophthalazine are attributable to its action in suppressing histaminase activity Administration of these drugs can control most cases of benign hypertension, but there remains an increment of malignant hypertension which remains unaffected. Schroeder (225) found that hydrazinophthalazine was most effective in patients with unsuccessful sympathectomy, malignant hypertension, and neurogenic hypertension The drug was relatively ineffective in renal hypertension. Chronic administration by mouth appeared feasible. Johnson and co-workers (226) found that hydrazinophthalazine frequently produced headaches and that oral doses of from 50 to 150 mg resulted in a significant reduction of arterial pressure. Tolerance to the drug was not uncommon. Persistent reduction of arterial pressure by the drug alone was rarely observed. Hydrozinophthalazine was most effective when used alternately with hexamethonium. It is possible that the former counteracts the renal effects of hexamethonium by the production of renal hyperemia (226).

Investigations on the use of veratrum alkaloids were continued The acute effects of intravenous administration of veratrum viride in patients with hypertension were studied by Stearns & Ellis (227). These authors conclude that intravenous administration of veriloid, a biologically standardized preparation of alkaloids from veratrum viride, has a place in the treatment of severe hypertensive disease, particularly during a hypertensive crisis Shapiro & Ferris (228) found a considerable variability in the response to intravenous administration of the drug. They compared the effect of vera-

tion of the arterial pressure, and then the drug was suddenly withdrawn, approximately one-third of the animals treated developed a sustained permanent hypertension. The authors suggest that the adrenal cortex normally secretes a pressor agent which is eliminated by the kidney.

Adrenalectomy has emerged as a new approach in the treatment of hypertension. The physiological changes which follow bilateral total adrenalectomy in patients with advanced hypertensive vascular disease have been described by Thorn and co-workers (245). In their report the relationship of adrenal cortical function to hypertension is summarized and the question is examined whether bilateral complete adrenalectomy is a feasible procedure in patients with hypertensive vascular disease. Procedures in the preparation and maintenance of the patients during and following operation are described It is concluded that patients with advanced hypertensive cardiovascular disease and cardiac and renal impairment are capable of undergoing bilateral complete adrenalectomy when adequately prepared and maintained with large doses of adrenal cortical hormone throughout the operation. All patients who survived operation showed a marked increase in the capacity to excrete sodium and chloride. In no instance has a fall in arterial pressure occurred without comcomitant sodium chloride loss. Zintel and associates (246) studied the effect of subtotal adrenalectomy in the treatment of patients with severe essential hypertension. They believed that subtotal adrenalectomy produced some beneficial effects on the objective and subjective signs and symptoms as well as a variable reduction in the arterial pressure of hypertensive patients. The possibility is considered that subtotal adrenalectomy may find its greatest usefulness as an adjunct to limited or extensive sympathectomy. The various types of operation on the sympathetic system were described by Sanford (247). As near complete denervation of the splanchnic bed as possible seems to give the most beneficial and enduring results Hypertensives should be considered for splanchnicectomy if they are true cases of essential hypertension, their hypertension is persistent and does not respond to adequate medical treatment, and the associated cardiovascular involvement is not so great that it contraindicates surgery. Contraindications to surgical treatment are evidence of marked renal impairment, cerebral deterioration, or severe cardiac damage The effect of sympathectomy for essential hypertension on the hallucal circulation has been studied by Mendlowitz & Touroff (248). It is believed that sympathetic nerve tone always returns to a variable extent after operation Furthermore, sympathectomy often produced an increase in intrinsic nonneurogenic vascular resistance. This could not be reversed by benzodioxane. Smithwick (249) reviews the effect of splanchnicectomy in hypertensive vascular disease. The prognosis of patients with hypertensive cardiovascular disease is significantly improved by thoraco-lumbar splanchnicectomy.

It is now well known that a pheochromocytoma can be the cause of persistent hypertension. Suggestions that the amounts of epinephrine and norepinephrine produced by the tumor may account for varying clinical pic-

persists after adrenalectomy for periods of at least four weeks. Despite the persistence of salt hypertension, cardiac hypertrophy begins to disappear. After adrenalectomy, however, salt hypertension disappears rapidly after substitution of tap water for hypertonic sodium chloride. Nephrectomy does not abolish salt hypertension. It is believed that the hypertension which develops after salt administration is dependent directly on the disturbance in fluid distribution and is not mediated through the adrenal gland or the kidney. Nye & Forrest (237) believe that only a severe restriction in salt produces the desired lowering of blood pressure and alleviation of symptoms in hyperpyesia. It is also necessary to adhere to the diet continuously. The British Medical Research Council has confirmed Kempner's main claim for the rice diet (238). About 70 per cent of cases of essential and chronic renal hypertension showed a good fall in arterial pressure, and a higher proportion obtained symptomatic relief. In some there was improvement in eye changes, heart size, electrocardiographic appearances, edema, and breathlessness The report also states that in renal failure, sodium restriction may be dangerous if the kidney's power to conserve the ion is impaired Mercurial diuretics in conjunction with a low-sodium diet can also cause serious sodium depletion. Corcoran, Taylor & Page (239) presented evidence that no dietary substance other than sodium had an effect on arterial pressure Strict adherence to the rice diet or measurements of output or urinary sodium were the only methods that insured adequate restriction of sodium.

The therapeutic effect of cation exchange resins was investigated by Gill & Duncan (240). The authors concluded that cation-exchange resins are effective adjuncts to diets low in sodium content but are no substitutes for them in the management of hypertension However, the sodium chloride can be increased to 1 to 1 25 gm. per day instead of the low levels of .2 to .5 gm needed with dietotherapy alone Deficiencies in serum calcium and potassium may be prevented by the administration of supplement of calcium lactate and potassium citrate. Page (241) found that one quarter of his patients respond satisfactorily to salt restriction.

The role of endocrine factors in hypertension has been discussed in detail by Perera (234). It is believed that an excess of circulating nor-epinephrine can be excluded as cause for hypertensive vascular disease. Nevertheless, the possibility still must be entertained that sensitization of blood vessels to normal amounts of norepinephrine could account for hypertension (242, 243) According to Perera, desoxycorticosterone raises the arterial pressure under all of the circumstances tested (234). However, the pressor response was faster and greater in adrenalectomized animals, in Addisonian man, or in the face of renal damage, than it was in normals and dissimilar to the response in hypertensives Patients with hypertensive disease invariably got an immediate small rise in arterial tension which was, however, transitory. Unlike desoxycorticosterone, no salt was required for the pressor effect of cortisone. Friedman *et al* (244) found that when desoxycorticosterone acetate was administered to rats in amounts sufficient to cause marked eleva-

be relied upon in the case of endocarditis. A complete eradication of the organisms must, therefore, depend on the chemotherapeutic agents. The sulfonamides, aureomycin, chloramphenicol, and terramycin are primarily bacteriostatic, whereas penicillin has a high bacteriocidal action. The usual laboratory sensitivity testing of organisms is based on the inhibitory or bacteriostatic action, and hence may be misleading in regard to choice of antibiotic in endocarditis. In this regard, Hunter has shown the marked difference in destruction of organisms in broth culture treated with penicillin and aureomycin although the inhibitory tests reveal the organism to be sensitive to both. Although streptomycin revealed no bacteriocidal activity on the broth cultures, it enhanced the bactericidal effect of penicillin when the two were given concurrently. The effect of combining penicillin with aureomycin, chloramphenicol or terramycin is somewhat variable. It has been shown that these agents may interfere with the early bacteriocidal effect of penicillin; on the other hand, the bacterial population may eventually be markedly reduced.

Friedberg (257) has analyzed a series of 148 cases of sub-acute bacterial endocarditis with 98 clinical recoveries and 50 failures. The recovery rate did not vary significantly with the sensitivity of the causative organism except with extremely resistant strains A fatal outcome in 50 cases was from failure to institute treatment because of error in diagnosis or inadequate and delayed treatment. Delay in diagnosis often resulted from failure to obtain a positive blood culture. It is stressed that a probable diagnosis should be made whenever there is unexplained fever of more than a week in a patient with an organic cardiac murmur. Although blood cultures should be obtained, treatment should be instituted while awaiting the report on the nature and the sensitivity of the organism Penicillin therapy of at least 2,500,000 units daily is advocated initially, and this is increased if it does not produce a satisfactory clinical response. Therapy may then be altered according to the organism isolated It is stressed that a good clinical response may be obtained with 3 to 4 gm. of aureomycin daily. A relapse is likely to occur within the first week after this antibiotic is discontinued, again suggesting that the bacteriostatic effect of aureomycin does not completely eradicate the organisms, although sterilization of the bloodstream may have been accomplished.

In addition to the problem of increasing bacterial resistance to antibiotics, there is an apparent increase in the number of cases of endocarditis attributable to naturally resistant bacteria such as the enterococcus group. Various authors incriminate the enterococci in from 4 to 20 per cent of the cases of coccal endocarditis. Flanders, McGee & Scott (258) review 30 cases of enterococcus carditis resulting from either *streptococcus fecalis* or *streptococcus liquifaciens*. Of these 30 cases there were eight apparent cures, two with aureomycin, two with penicillin, two with streptomycin, one with penicillin and streptomycin combined, and one successfully treated with bacteriophage. Rubenstein & Austin (259) report a case of endococcal endocarditis in which cure was effected by a combination of terramycin and aureo-

tures and drug responses have refocused attention on the battery of pharmacological diagnostic tests available. Case reports showing both false positive and false negative results of the tests have been recorded in the literature. Some of these apparent failures may be accounted for on the basis of technique, drug dosage or both. Anderson, Rolufs & Doerner (250) review the pharmacological tests and emphasize the importance of evaluating a battery of such tests rather than any single test. Evans *et al.* (251) have re-evaluated pharmacological and cold pressor studies in a series of hypertensive patients. Pharmacological agents studied include both substances which cause or produce a typical attack (histamine, methacholine and tetraethylammonium chloride or adrenergic blocking agents). They emphasize the importance of establishing a basal arterial pressure recording over a period of time before any of the tests are attempted. Technique and drug dosage in each case are indicated. Anderson *et al.* (250) obtained a negative methacholine test in a proven case of pheochromocytoma. Mason (252) reports two proven cases of pheochromocytoma with a false negative benzodioxane test but with positive combined benzodioxane-hisatmine tests in which the benzodioxane effectively blocks the pressor response of histamine. In each of these cases, preoperative laminograms indicated the location of the tumor.

Endocarditis

Acute endocarditis.—Dowling *et al.* (253) reported that staphylococci are now being recognized more frequently in all types of endocarditis. In their series of 76 cases, pre-existing cardiac damage was present in 42 per cent. Staphylococcus aureus was isolated in 64 cases, staphylococcus albus in 12, and there was essentially no difference in prognosis with the two types of staphylococci. Fifty-two per cent of the patients in this series recovered with penicillin therapy Pre-existing infections of skin, subcutaneous tissue, localized abscesses, osteomyelitis, puerperal sepsis, and unsterile intravenous injections, particularly in narcotic addicts, were frequent predisposing conditions. Early initiation of high doses of antibiotics at the clinical suspicion of endocarditis is indicated and therapy is then adjusted in regard to the sensitivity of the isolated organism.

Four cases of acute endocarditis complicating bacterial pneumonia were described (254). The early recognition of endocardial lesions are emphasized. Each of the four fatal reported cases were associated with rapidly progressive heart failure and murmurs of aortic incompetence. Three cases showed ulceration of the aortic valve at autopsy.

Sub-acute bacterial endocarditis—Although the improvement in the prognosis of patients with sub-acute bacterial endocarditis since the advent of chemotherapy has been dramatic there is still an approxiamte 30 per cent [illegible] of en- [illegible] e other [illegible] agents and natural and acquired defense mechanisms of the host, the latter cannot

similar tracings were often obtained in normal subjects. Kjellberg & Rudhe (269) have described a characteristic pulmonary artery tracing in cases of pulmonary stenosis characterized by a slowly rising ejection curve with reduction of the secondary waves.

Intraluminal aortic pressure curves and electrokymographic densograms and border tracings of the aorta have been compared by Salans *et al.* (270). It was concluded that the general contours of the pressure and electrokymographic curves are similar but that cardiac events are not simultaneously recorded by these two methods. The disadvantages of the electrokymograph as regards time lags and frequency responses may be corrected by improvements in the instruments, as described by Morgan & Sturm (271).

BALLISTOCARDIOGRAPHY

Ballistocardiography continues to enjoy a widening field of clinical application. The more portable direct pickups have a somewhat wider use than the table types. Brown *et al.* (272) review the various types of apparatus used. They analyze their findings in normal and in abnormal states, as studied with the modified high frequency table. With the commerciably available or readily assembled direct ballistocardiographs, the tracing may be recorded as velocity, displacement, or an integration of the two. Smith & Bryan (273) point out the importance of understanding the characteristics of the type of pickup used in terms of frequency response, linearity of motion, and phase shifts. Gubner (274) as well as Blackman (275) describe methods by which the R-wave of the electrocardiograph may be superimposed on the ballistocardiographic tracing in a one-channel recording machine Brandt and co-workers (276) introduce the tricardiograph, a film which records a slit kymogram of the heart border and simultaneous electrocardiograph and ballistocardiograph oscillographic records. They suggest its use as a rapid screening method in cardiac studies There is no doubt that this method will become extremely valuable. Starr & Hildreth (277) have published ballistocardiographic follow-up studies on 80 subjects originally observed 10 to 14 years previously as part of a normal standard series Sixty-five continued in good health and their records were re-studied from the standpoint of the effect of aging on the ballistic record. The principal effect noted was a steady diminution in detph of the I-wave with a lesser diminution of the J-wave. No change was noted in the duration of the waves as age advanced In young persons, these changes of age take place slowly with a somewhat accelerated rate after age 50 Taynor *et al* (278) utilizing a direct photoelectric ballistocardiogram, have studied 195 patients referred for cardiac study. Ballistocardiographic and electrocardiographic records were taken before and after a two-step exercise test Ballistocardiograms were judged on the basis of amplitude of component waves and abnormalities of contour Seventy of 75 subjects with positive two-step tests had abnormal ballistocardiograms and six of those seven with borderline two-step tests had abnormal ballistocardiograms. Twenty-seven patients of 113 with

mycin after failure with penicillin and streptomycin. The clinical course suggested that the response was primarily a result of terramycin. Friedberg (260) reports a series of 11 patients with sub-acute bacterial endocarditis treated with 4 to 6 gm. daily of aureomycin. The organisms isolated included *streptococcus veridans* and *streptococcus fecalis;* in the remainder, blood cultures were negative. Aureomycin effected the cure in two patients with positive blood cultures, one of which had previously relapsed following therapy with penicillin and streptomycin. Some of the patients who failed to respond to aureomycin were subsequently cured by penicillin or by a combination of antibiotics. Aureomycin failed to influence subacute bacterial endocarditis caused by enterococci. It was found that aureomycin therapy was usually followed by a prompt clinical improvement, with restoration of normal temperature and negative blood cultures. Within three to seven days after stoppage of the drug, however, fever and positive blood cultures recurrred Consequently, aureomycin is regarded as an adjunct to penicillin treatment; it is indicated only when treatment with penicillin has failed to produce a clinical response or when penicillin-resistant organisms are known to be involved. The effect of chloromycetin was investigated by a series of authors (261, 262).

Perry, Fleming & Edwards (263) report 52 autopsy studies of patients succumbing to sub-acute bacterial endocarditis or its complications. The most prominent lesion present in 90 per cent of the cases were miliary infarcts. Other lesions included interstitial and perivascular cellular infiltrates, scars, or emboli with Ashoff nodules present in only 10 per cent. Treated and untreated cases were essentially indistinguishable. There was no significant correlation of incidence of myocardial lesions and cardiac failure.

Electrokymography

Dark & Paley (264, 265) and Heyer & Boone (266) have reviewed electrically recorded movements of the heart (the electrokymogram) in cardiac disease. The normal contour and timing of the electrokymographic tracings were also discussed. The interpretation of abnormal pulsations, of course, depend on thorough familiarity with the normal variations, particularly in regard to the portion of the ventricular silhouette studied. Davies & Venning (267) have emphasized these variations and compared them with abnormal tracings. Although shape and positional motions of the heart may make it difficult to interpret cardiac volume changes, they offer an interesting and unique method of studying the complex nature of contraction and relaxation of the heart.

Soloff, Zatuchni & Stauffer (268) have studied the atrial border tracing with particular reference to mitral regurgitation and noted the variation in atrial tracing in normals and the dangers involved in interpreting a single tracing from an atrial region. They report the so-called plateau curve of organic mitral regurgitation in subjects with apical systolic murmur. However,

formed by the reviewer. It was found that angiocardiography was of no significant diagnostic aid. An adventitious sound in early diastole was present in at least half of the patients. The same author describes the electrokymographic findings in this disorder (285) It is believed that the finding of "flat-tops" is highly diagnostic of chronic constrictive pericarditis. It appears that the early diastolic dip of the right ventricular curve occurs during the rapid filling phase. Ballistocardiographic findings were discussed by Scarborough *et al.* (286). The chief abnormality was the presence of large abnormal early and mid-diastolic waves. In experimentally produced pericarditis, sodium, chloride, and water balances were markedly positive during the acute and chronic stages (287). It appears peculiar that there was no correlation between the level of glomerular filtration rate and salt and water retention A case of constrictive endocarditis (parietal fibroplastic endocarditis) in an adult has been studied (288). There was dense thickening of the endocaridum without involvement of the valves The clinical picture in this patient was precisely that of chronic constrictive pericarditis

The myocardium may be involved in pericarditis. Godfrey (289) reported on three cases of acute nonspecific pericarditis in which clinical and electrocardiographic evidence of significant myocardial injury was present. The possibility exists that acute nonspecific pericarditis may be followed by prolonged and perhaps permanent myocardial injury, and the electrocardiographic changes seen in constrictive pericarditis may be due to myocardial ischemia. Ischemia may result from interference with the blood supply to the superficial myocardium as a result of compression by the intrapericardial fluid under pressure. Herrmann and associates (290) believe that aureomycin or terramycin may be considered as worthy of trial in patients with acute idiopathic or nonspecific pericarditis

Carcinomatous involvement of the pericardium as part of widespread metastases is not frequent Constrictive pericarditis produced by such pericardial infiltration during the clinical course of metastatic carcinosis is very rare Slater and associates (291) report a case of chronic constrictive pericarditis produced by diffuse metastatic carcinoma or the pericardium In their patient, the pericardial carcinoma was the only metastasis from a primary breast carcinoma completely resected 14 years previously Bierman and associates (292) report on four cases of leukemia in which pericarditis appeared as a serious complication and contributed toward death in three of these patients Electrocardiographic changes in these patients were characterized by tachycardia, low voltage, elevation of ST complexes, and flat to inverted T-waves

Typical right ventricular pressure tracings recorded in patients with constrictive pericarditis have been published by Tybjaerg-Hansen (293). It was found that the characteristic tracing obtained in this disease was not an artefact since it could be obtained by direct puncture of the left ventricle during operation The curves may revert to normal following operation The author believes that interference with diastolic dilatation is the main factor in the

negative two-step tests had abnormal ballistocardiograms either at rest or after exercise. In another study, Moser *et al.* (279) observed ballistocardiograms of 100 patients who had myocardial infarction, as demonstrated either by the electrocardiogram or by clinical history. Of these subjects, 81 presented abnormal ballistocardiograms at rest, while 19 had normal tracings. Several types of abnormalities in tracings were encountered. Patients with angina pectoris following an infarction had a high percentage of abnormal ballistocardiograms. There was no correlation between the type of ballistocardiographic abnormality and the severity of the clinical condition of the patient.

Pericarditis

Tuberculous pericarditis, its treatment with streptomycin, and some observations on the natural history of the disease were discussed by Myers & Hamburger (280). Their patients were divided into two groups In the first were five patients who died shortly after admission of cardiac failure or extensive pulmonary or miliary disease In the second group were four patients who showed definite evidence of pericardial healing and who, for relatively long periods, were completely asymptomatic, only to return later with tuberculosis in some other part of the body. The difference in the course of the disease between the two groups are described It is believed that the duration of the fever rather than the speed of healing is a criterion for the efficacy of streptomycin therapy. This is because several patients with pericarditis healed without the help of streptomycin The average of less than 13 weeks of fever in the treated group compares favorably with the average of more than 21 weeks in the untreated group. However, Falk & Ebert (281) showed that streptomycin is by no means universally effective in this disease A critical pre- and postoperative study of 61 patients with constrictive pericarditis operated for chronic cardiac compression was presented by Chambliss and associates (282) The operative mortality as well as the results obtained were discussed Tuberculosis was the cause of pericarditis in 28 per cent In most of the remaining cases, the etiology was obscure The authors report on the symptoms, physical signs, and laboratory examinations The frequent confusion of nonspecific pericarditis with myocardial infarction was stressed by Gilley and associates (283). The clinical features which distinguish this disease from acute myocardial infarction are chest pain which is aggravated by deep respiration, pericardial friction rub, associated respiratory infections, and a tendency for recurrent attacks. Naturally, the prognosis is more favorable in nonspecific pericarditis than in myocardial infarction It is stressed that one electrocardiogram alone offers very little positive help in the early diagnosis of nonspecific pericarditis However, serial electrocardiograms are usually diagnostic The *Johns Hopkins Bulletin* had published a volume on clinical and laboratory findings of constrictive pericarditis. In this volume, McKusick (284) described the clinical features of 25 patients with constrictive pericarditis. In 16 of these, catheterization was per-

in future medical discussions to separate the psyche from the soma or to overemphasize either one.

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abnormal hemodynamics of this condition. The systolic contraction of the heart is relatively unimpaired. This would mean that the residual volume of blood in the right ventricle remains normal. This assumption is supported by the findings of the reviewer (294).

Peripheral Vascular Disease

Starr (295) has summarized physiologic facts in the pathogenesis and treatment of obstructive vascular disease. Modern conservative measures used in the treatment of peripheral vascular disease of the obstructive type are discussed. The author deals with the effect of pumping devices, heat and cold, and reflex and surgical vasodilatation. Starr states that the proper therapeutic aim is to maintain the temperature of an extremity with obstructive vascular disease at the level at which the relation of demand to blood supply is most favorable. Edwards & Crane (296) believe that sympathectomy has been almost invariably of use in the treatment of patients suffering from arteriosclerosis of the lower extremity. A moderately unfavorable influence was exerted by the presence of diabetes. Intra-arterial 2-benzyl-2-imidazoline hydrochloride (priscoline) therapy for peripheral vascular disturbances was discussed by Lippmann (297). It appeared that intra-arterial 2-benzyl-2-imidazoline hydrochloride enhanced the vasodilator response to heat in cases with Raynaud's attack. Contraindications to the therapy are the development of systemic reactions after intra-arterial injections of 10 mg priscoline. The peripheral vascular lesions of lupus erythematosis were discussed by Lowman & Slocumb (298). The vascular pattern of reaction on the venous side of the circulatory system, consisting of edema, cellular reaction, and sclerosis is described. It appears that the polymyositic and perineuritic nodules of lupus erythematosis are identical to those seen in rheumatoid arthritis and that both are produced in this vascular pattern of reaction. There is no clue as to whether the vascular reactions in lupus erythematosis are secondary to damage by an extraneous factor, or whether a hyperergic response is affecting injury to a responding system. An exercise test in intermittent claudication has been described by McDonald & Semple (299). The authors used an automatic oscillograph to study variations in the pulsations and pressure in the blood vessels of the extremities. It was found that pulsations in limb vessels after moderate exercise increase or remain the same in normal subjects, but that they decrease in those with intermittent claudication The value of these findings of this "inverse reaction" in patients with intermittent claudication is discussed.

It is fitting to conclude this review with two papers published toward the end of 1951 dealing with some of the most important general aspects of [illegible]

a friendly, beneficent attitude of the physician toward his patients in relation to his community to problems of national health and to international relations. This will do more than anything, White says, to make it unnecessary

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DISEASES OF THE KIDNEYS[1]

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The Renotrophic Effects of Steroid Hormones

Studies of the influence of steroid hormones on the kidney go back to 1930. In that year, Korenchevsky (1), systematically studying the effects of castration of male rats, found late renal atrophy after removal of the gonads, with further observations reported four years later (2). A "male hormone" extract of urine would restore the kidney (3), as would testosterone and estrogen (4, 5). These observations, confirmed for the rat with related androgens (6, 7), were reviewed by Korenchevsky & Ross in 1940 (8). The effects are not constant among species, however. For example, in 1940 Selye (9) obtained some hypertrophy with testosterone propionate in normal rats of both sexes, applying the word renotropism for this phenomenon, but he and Albert (10) two years later [as had MacKay (11)] had been unable to confirm this. Further, Ludden, Krueger & Wright (12) found that the dose of testosterone propionate has an optimum level beyond or below which the response is diminished, an observation similar to the recent one of Leathem (13) who was able to restore renal weight after castration in rats with small doses of testosterone propionate but who found larger doses less effective. There is a normal sex difference among animals; for example, the kidney in the male mouse weighs 15.2 mg. compared to 12.9 mg. in the female [Warren (14)], and in the human being the male kidney is 11.6 per cent larger than the female (15). Histologically, the effect is by increase in size of the proximal and distal convoluted tubule with thickening of the cortex (16). The epithelium of the glomerulus is thickened also to conform more closely to the male type (17), although this has been questioned (15, 18) The tubular diameter is increased by 20 per cent in rats and from 7 to 17 per cent in dogs (15).

Androgens administered along with estrogens show an additive effect (18, 19). Testosterone propionate will in part replace the renal atrophy following hypophysectomy (16). The compensatory renal hypertrophy produced by unilateral nephrectomy is enhanced by testosterone propionate (to 98 per cent of the weight of both kidneys compared to 76 per cent without treatment) (15), and retarded by hypophysectomy (20, 21) Removal of the gonads, on the other hand, has no influence on it (11).

After the last war, interest in renotrophic effects was increased, when the present review begins The reports since 1948 have been roughly divided into four main groups: (*a*) the exact cellular response of the kidney (hypertrophy versus hyperplasia); (*b*) the effect of testosterone and estrogens on

[1] The survey of literature pertaining to this review was completed in October, 1952

the normal kidney and on normal renal function; (*c*) the effect of cortisone and of the pituitary especially by way of ACTH on the kidney; and (*d*) the clinical applications of the renotrophic effect.

Renal Hypertrophy versus Hyperplasia

As early as 1913, Morel & Verliac (22) had studied the rat kidney undergoing compensatory hypertrophy after unilateral nephrectomy, and concluded that the increase in weight could not be explained by cellular hyperplasia. Since that time, hypertrophy has been considered to be the chief process. The microscopic changes consist of hypertrophy of the epithelium of the proximal and distal convoluted tubules, and the lining of the glomerular capsule (23).

That mitotic figures are infrequent in the normal kidney is well known and can be explained by its slow rate of growth. Sulkin (24), studying the results of unilateral nephrectomy in 90-day old rats, found the peak of mitotic activity 72 to 240 hr. after operation. This peak coincides with the weight curves of Morel & Verliac mentioned earlier, which showed a 32 to 37 per cent increase in the 4 to 10 day period and 9 to 16 per cent increase in the 10 to 20 day period. The experimental kidney showed an increase in binucleate cells (polyploidy) and a similar increase in the frequency and magnitude of large nuclei. However, the ratio between cortex and medulla remained constant. Sulkin concludes that the enlargement is because of hyperplasia in contrast to the deduction of the French authors that it was simple hypertrophy.

Rollason (25), using younger animals (rats at 14 days of age), found evidence of hypertrophy in addition to hyperplastic signs, for the tubular diameter increased within the first 24 hours after nephrectomy The increase in mitotic figures he found limited mainly to the second day, but agrees with Sulkin in the finding that they were the same in both cortex and medulla He was unable to find any initial pseudohypertrophy (edema) which had been suggested by previous authors These studies are pertinent because of the negative data obtained by Korenchevsky & Ross (8) and Lattimer (15) following androgen administration. These workers reported few mitotic figures with the renal enlargement following testosterone administration. The conclusion seems apt that enlargement from androgens is by hypertrophy rather than hyperplasia.

Steroid Hormone Effects on the Normal Kidney

Enzymes.—Dunn (26) showed that while the proximal convoluted tubule [illegible] phosphatase, [illegible] 1945, Kocha- [illegible] nechanisms of hormone action on the kidney. They had found (28, 29) that testosterone propionate in mice decreased renal "alkaline" phosphatase and increased the "acid" phosphatase, and that other androgens caused similar alterations.

The degree of change paralleled the amount of renal hypertrophy, except in early stages which showed slight increase in "alkaline" phosphatase. Rats had, on the contrary, increased "alkaline" phosphatase.

In 1948, Kochakian (30) rounded off this work by finding that "alkaline" phosphatase decreased progressively from the distal end of the proximal convoluted tubule as the glomerulus was approached, with a slight increase in concentration at the glomerular end. He suggests that

> if the enzyme is involved in the reabsorption of certain materials [see Lundsgaard (31)], then these substances are not only filtered through the glomerulus in smaller and smaller quantities, but also that they are being reabsorbed as rapidly as possible under androgen stimulation for presumably anabolic purposes.

Here is a tie-up between the androgens' renotrophic action and their protein anabolic quality. Other evidence was found by the same workers among other enzymes [Kochakian (32)]. Testosterone propionate increases the D-amino acid oxidase of the mouse kidney. Renal arginase too is increased by various steroids, methyl testosterone being most potent (632 per cent increase) perhaps because it acts most rapidly, but the arginase is increased in relation to the dose rather than to renal size As Kochakian & Robertson (33) indicated, the fact that testosterone is so potent at restoring the reduced arginase and alkaline phosphatase of the rat kidney after hypophysectomy shows that the action is not mediated through the pituitary, nor the adrenal [Kochakian & Vail (34)] These changes in arginase concentration occur with doses of androgen too small to cause an accompanying increase in renal weight. It was Kochakian's suggestion that these changes were evidence of protein anabolic activity rather than a specific renotrophic effect, and that perhaps the anabolic properties of the androgens are at least in part mediated through the kidney.

Nitrogen retention —Leathem (13), studying castrate rats, found no increased nonprotein nitrogen after gonadectomy, but found that nitrogen retention occurred if testosterone propionate were given (the normal NPN of 54 mg /100 cc rose to 96 mg /100 cc with doses of 25 mg daily). Similar, although less marked, increases occurred in normal animals (to 68 mg /100 cc. with 2.5 mg. daily).

Van Bekkum & Kassenaar (35) gave castrate female mice doses of 2.5 mg. of testosterone propionate twice a week. The blood urea nitrogen almost doubled after 40 days of treatment, reaching uremic levels. Histologically, they saw hypertrophy of the convoluted tubule cells, accompanying the two-fold renal hypertrophy, and glomerular shrinkage with patchy mononuclear infiltration Kochakian, Robertson & Bartlett (36), however, found no increase in nonprotein nitrogen after 13 days' treatment of the castrate rat with 1 mg of testosterone propionate daily

Nitrogen retention has also occurred clinically, although under special conditions Herrmann, Kirsten & Krakauer (37) gave androgens and estrogens to four patients immobilized with carcinoma Hypercalcemia resulted

in nephrocalcinosis which in turn caused renal insufficiency. These toxic episodes were corrected by stopping treatment. Similar treatment did not cause this sequence if the patients were ambulatory. Caution is needed in using androgens clinically.

The "wearing-off" effect is of interest. Kochakian (38) found a return to normal blood nitrogen levels after about two weeks of androgen administration to rats in normal nitrogen balance, a fact which had not previously been noted. Similarly, the animal's body weight increased, only to fall off after the same interval. This he called the "wearing-off" effect. The same phenomenon occurred in the normal (39) and hypophysectomized (40) female rat. After adrenalectomy (41), the typical "wearing-off" effect occurs. Testosterone propionate causes nitrogen retention (as well as electrolyte retention) in adrenalectomized animals, so proving that its action is not mediated by the adrenals. By increasing the dose of androgen, this effect can be delayed [cf the similar effect of growth hormone (42)]. Braasch *et al.* (43), observing that testosterone propionate caused a lessened rise in nitrogen excretion after thermal burns in rats, found that after 18 days in the female rat and 12 to 14 days in the male rat the effect of the drug wears off. A relation to vitamin deficiency has been suggested (36).

Renal function.—Clearance studies in various animals and in man have shown that certain functions increase with testosterone induced renal hypertrophy, while others are not affected. For example, Welsch and associates (44) found in the dog that testosterone propionate doubled the diodrast maximal tubular excretion (Tm) but had no effect on glomerular filtration or on renal plasma flow. Lattimer (15) noted increased inulin clearance in addition to the increased diodrast Tm in rats and dogs, and obtained additional renal hypertrophy with testosterone in man after unilateral nephrectomy. Dean, Abels & Taylor (45), however, could see no increased tubular function in normal man with testosterone. Klopp, Young & Taylor (46), giving large doses of testosterone and testosterone propionate, found no significant increase in glomerular filtration, renal blood flow, Tm_{PAH} or Tm_{GLUC} in four normal men and five with decreased renal function.

Richardson & Houck (47) in a recent study of testosterone propionate on normal female dogs, obtained little positive data. There was little or no effect on the renal tubular mechanism for resorption of sodium, chloride or potassium ions. The maximum tubular excretion for paraminohippuric acid was unchanged, and renal cytology and renal weight were not influenced. Estradiol, on the other hand, decreased the filtration of potassium and markedly decreased the maximum tubular excretion without affecting the glomerular filtration rate. No microscopic or weight changes were seen. However, since no renal hypertrophy was obtained in these animals, we are not actually dealing with changes in function with renal hypertrophy itself.

Androgenic versus renotrophic activity.—Following Kochakian & Murlin's (48) finding that androgens have a pronounced protein anabolic effect,

Korenchevsky & Ross (8) suggested that these substances have differential potencies of androgenic and protein anabolic activity. This has been demonstrated by Kochakian (49) and by Beland, Masson & Selye (50). Kochakian in a series of papers (32, 49, 51, 52) amplified the data hoping to find a protein anabolic steroid with little sexual effect. He found that the polar groups influence the relation between renotrophism and androgenic qualities. A 17,β-hydroxyl group gives maximal renotrophic effect while an unsaturated 3 ketone group gives the most androgenic effect. A 3,α-hydroxyl group reduces androgenicity but not renotrophism, and a 3 keto group enhances androgenic activity but has no effect on renotrophic properties But in none of the compounds studied were the two effects completely separate. Attempts to find such a substance by testing compounds with only one polar group failed because of the insolubility of the compounds (53). Perhaps the second polar body is essential for physiologic activity. It may be that the metabolic breakdown products of the administered androgen are more responsible than the androgen itself for the production of physiologic changes

Methylandrostenediol is of particular interest to the clinician because of its great protein anabolic qualities and less pronounced androgenic properties (54). The review of Henderson & Weinberg (55) is helpful. First synthesized by Ruzicka in 1935, methylandrostenediol is structurally most closely related to methyltestosterone, the difference being an alcohol rather than a ketone radical at carbon 3, associated with the characteristic shift of the double bond from 4:5 to 5.6, as follows: (Figure 1). The intensity of its

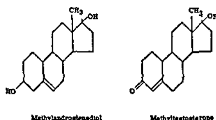


FIG 1. A comparison of the structural formula of methylandrostenediol and methyltestosterone

several properties varies in animals depending on route of administration, but not in the predicted fashion Rather, the oral route seems to potentiate its weak androgenic activity, whereas parenterally the protein-anabolic property is accentuated. This peculiarity seems to be a concrete illustration of the fact that, since different metabolites of varied activity are formed

the androgenic activity is less than one-eighth that of testosterone propionate. The protein-anabolic activity, on the other hand, is one-fifth that of testosterone, the difference permitting anabolic therapy without masculinization. For instance, it has been used in the treatment of 24 cases of female breast cancer (57, 58) in doses up to 100 mg. per day parenterally with masculinizing effects in only one patient (some growth of facial hair).

Adrenal Cortical Hormones and Renal Function

There is no need to repeat here the material on the effects of cortisone and ACTH on the normal and diseased kidney contained in the complete review by Luetscher in last year's *Annual Review of Medicine* (59), but we can supplement it with a few additional references.

Gross & Meier (60), studying the effects of cortisone on the remaining kidney of hypophysectomized rats, found increased compensatory hypertrophy with doses of 1 and 5 mg. every other day. On the other hand, 11-desoxycorticosterone and 11-desoxy-17-hydroxycorticosterone (Compound S) had no such effect. Hall & Hall (61), also studying unilaterally nephrectomized rats, found that although the antianabolic effects of cortisone were less on the kidney than on the body tissues, there was still less compensatory renal hypertrophy in the treated animals than in the controls The kidneys of the intact rats, however, increased 25 per cent in size on cortisone therapy.

The effect of stress has been studied further. Leduc & Guillemin (62) subjected rats to low temperatures (5 or 10°C) for from 6 to 48 hr. to find that while the dry weight of the carcass and most organs decreased, there was no real change in the weight of the heart or brain, or of the kidneys. Constantinides (63, 64) injected formalin into rats, subjected them to cold, or provided forced exercise, and found that renal mitoses and enlargement occurred with each of the stimuli. Formalin injection (19 6 per cent rise in renal weight) was more effective than cold (14 per cent rise) which in turn was better than exercise (only 7 per cent enlargement). Simultaneous increases were noted in the weight of the adrenal glands The renal effects were inhibited by adrenalectomy. The number of mitotic figures, which were limited to the proximal convoluted tubule, increased by 120 per cent after exposure to cold, but only by 11 per cent if the adrenal glands had been removed. The renal changes occurred as early as 20 hr. after the stress had been applied. These findings show the adrenal to mediate the renotrophic effects of such stresses.

Renal function in the hypopituitary patient is decreased. Luft & Sjögren (65) found low glomerular filtration rate and renal blood flow in a patient with panhypopituitarism Treatment with desoxycorticosterone acetate and testosterone propionate increases both these functions, but so does subsequent administration of thyroxine. In another report (66), they studied 17 cases (three cases of postpartum pituitary necrosis, six cases of chromophobe adenoma, and eight cases of acromegaly). In only the patients with acro-

megaly did they find normal renal function (? because of the presence of increased growth hormone: cf. Selye's suggestion of increased renal function from growth hormone). In the other nine patients, they found that desoxycorticosterone acetate and salt augmented the filtration rate without alteration of the renal blood flow. Thyroxine often increased renal blood flow, as well as increasing the glomerular filtration rate, sometimes only if given with desoxycorticosterone acetate.

In patients with Addison's disease, the glomerular filtration rate was decreased but the renal blood flow was greater than in patients with hypopituitarism, which suggested that the hormonal control of renal function was a result of factors other than those in the adrenal cortex, such as the thyroid, as the authors suggest.

Similar findings concerning blood flow and filtration rates were obtained by Pickford & Watt (67). They studied six patients with chromophobe adenomas to find that the loss of the anterior pituitary gland produces inability to excrete a sudden water load (associated with a decrease in glomerular filtration rate and renal blood flow) which is not attributable to nervous changes or actual renal damage In six patients with acromegaly, they found no increased clearances, nor had others (68). White *et al.* (69) shed some light on Selye's concepts of the effects of growth hormone on the kidney, mentioned earlier. They found that adrenal replacement therapy, which is adequate for the adrenalectomized dog, is not enough after hypophysectomy. Consequently, the decrease in renal function after removal of the pituitary gland is not because of adrenal insufficiency or the loss of thyrotrophic or adrenotrophic hormones, nor does ACTH have a renal effect in hypophysectomized dogs The conclusion is that the kidney is supported by growth hormone The same authors (70) gave growth hormone to hypophysectomized dogs It raised the previously depressed renal blood flow and glomerular filtration rate and the PAH maximum tubular excretion rate. In the [illegible]

diuresis in Addison's disease is because of an inherent inadequacy of the renal tubules, secondary to adrenal insufficiency Slessor & Thorn (72) and Thorn *et al.* (73) in fact, found that this diuretic response can be restored with cortisone.

The Effect of Steroid Hormones on the Diseased Kidney

That testosterone could exert a protective influence on the kidney was suggested by Selye in 1940 (74), when he found that the degenerative changes in the mouse kidney from sublimate intoxication were not seen in animals receiving testosterone Feyel (75) repeated the general plan of Selye's earlier experiments. Páll & von Györy (76) had contrary results After poisoning rats with sublimate of mercury, they assayed the renal damage by measurement

of blood nonprotein nitrogen and blood chlorides. Greater histologic, as well as chemical, defects were seen after "protective" treatment with male or female sex hormones than were shown by the controls. They consequently advise against their use in renal disease.

In this connection, the relation of glucuronidase activity to renal damage and repair is of interest. Eschenbrenner & Miller (77) had found that chloroform produces renal necrosis in male mice at lower doses than in the female or castrate male animal. Kerr, Campbell & Levvy (78) had noted higher levels of glucuronidase activity in the kidney of male mice treated with chloroform than in a similarly treated female kidney, presumably because of the more rapid cell proliferation after injury. Carbon tetrachloride, aminopterin, and cortisone showed the same sex difference. The recent study by Morrow *et al.* (79) showed that normal male mice have from 1.3 to 2.6 times as much glucuronidase activity as the normal female and that castration will lower the normal male level to that of the female. Consequently, the attribute involved in reparative processes (high glucuronidase activity) actually renders the kidney more suceptible to damage by chloroform. This is at variance with Selye's conclusions with mercury poisoning.

Selye & Friedman (80) in 1941 showed that atrophy of the mouse kidney after ligation of the ureter is inhibited or delayed by large doses of testosterone. Weinstein *et al.* (81), repeating Selye's experiments two years later, found a beneficial effect of testosterone in female rats, in that there was inhibition of renal atrophy and stimulation of renal hypertrophy. Estrogens had no such effect but did increase renal vascularity.

Homburger, Forbes & Desjardins (82), in extending Selye's work, used mice to evaluate the relative renotrophic potency of various steroids Their power to protect the kidney during experimental hydronephrosis (measured by the histologic changes of renal repair) was compared with their androgenic activity (by clitoral weight). With the normal kidney, renal enlargement roughly paralleled clitoral hypertrophy for most of the steroids tested. But in addition, testosterone propionate and methylandrostenediol had a greater effect on the diseased kidney than either on the clitoris (the androgenic effect) or on the healthy kidney (the classical renotrophic effect), which could indicate a separate protective action of those substances. No such differential action was observed for testosterone, vinyl testosterone, testosterone tocaptate, or testosterone carbonate

Their technique was to ligate the left ureter of mature female mice, then inject 2.5 mg. of the steroids daily into the animals for from 30 to 40 days, with suitable controls They confirmed the finding that contralateral compensatory hypertrophy is increased by testosterone propionate. In the control obstructed kidney, after 25 days the cortex was a mere shell with foci of round cell infiltration and scattered distended glomeruli. In the animals treated with the maximally protective androgen, the tubules formed islands surrounded by fibrous tissue, and their cells were often multinucleated, indi-

cating actual proliferation. In 1948 several papers were published in Europe describing the application of the experimental findings to established renal disease, in contrast to the protective, preventive action uncovered in the animal experiments. The results can be abstracted, although most series could not be adequately controlled.

Imbriano (83, 84) treated six cases of chronic nephritis with testosterone propionate in total doses varying from 900 mg to 300 mg. Whereas tubular reabsorption in response to antidiuretic hormones was abnormal before treatment, it returned to normal values at the end. Proteinuria was cleared in two patients and decreased to a trace in the other four, and red blood cells and casts similarly disappeared. Elevated nonprotein nitrogen levels, present in two patients, returned to normal, as did the creatinine levels He concludes that testosterone will improve deranged tubular function if glomerular filtration is not too grossly abnormal.

Cavalleri & Vittone (85), studying similar cases, treated 4 patients with 100 mg. of testosterone. They, however, noted little significant change in blood pressure or urinary output. Patrono & Pincelli (86) found likewise, after treating 6 patients with advanced renal disease with 100 mg. doses of testosterone propionate implanted subcutaneously, that they could not advocate such treatment on a wide scale for chronic renal disease

Giordano & Perri (87), in their series of patients with chronic nephritis, were unable to report any real improvement after testosterone therapy; in fact most of the patients became worse, with rising blood nitrogen levels.

Langeron, Nolf & Liefooghe (88, 89) observed no effect of testosterone therapy of patients with chronic parenchymal renal disease. Their glomerular filtration, tubular water reabsorption, and urea clearance were unchanged, even though testosterone had a generally beneficial metabolic effect. In one reported case, however, a blood nonprotein nitrogen level of 93 mg /100 cc was reduced to 51 with 5 mg of testosterone propionate daily for 10 days When the nonprotein nitrogen rose again after two months, administration of another 100 mg reduced it to 60 mg /100 cc. ("wearing off" effect?)

Matassarin (90) reported on 6 of a total of 50 patients who were treated with testosterone propionate with reduction of blood non-protein nitrogen levels and clinical improvement. However, most had additional treatment (fluids, intubation, catheterization, etc.) and the group was made up of patients with diverse diseases (prostatic as well as intestinal obstruction, etc.) The experience of others (91) is also open to such objections.

Klotz & Debray (92, 93), Justin-Besançon, Klotz & Cournot (94) and Justin-Besançon & Klotz (95) had good results from the administration of testosterone to hypogonadal patients [cf. the studies of Luft & Sjogren (65, 66) and Pickford & Watt (67) previously cited] One patient, a man with pituitary hypogonadism, was given 500 mg. of testosterone by implantation. His mild azotemia, urinary casts, and diminished phenolsulphoaphthalein (PSP) excretion gave way to mannitol clearances and Tm_{PAH} which were

above normal, and to the disappearance of the casts. A second patient with a similar endocrine defect had albuminuria, casts, and azotemia. After treatment, his blood urea nitrogen was 40 mg /100 cc., urea clearance 63 and 72 cc./min. and PSP excretion 62 per cent, and his casts disappeared. They also treated 11 other patients with diverse nephropathies: of the total 13 patients, 6 were unchanged, 1 was improving and 6 were better. In a reply to the paper of Klotz & Debray (92), however, Mayer & Bloch (96) reported three such cases similarly treated with total doses of testosterone propionate from 110 to 28 mg. without significant effect. We must conclude that the results in chronic nephritis are equivocal at best.

It was Henderson and co-workers (97) in 1948 who drew our attention to the clinical possibilities of testosterone therapy for anuria. Twenty-seven patients with anuria secondary to severe cholera were studied. Testosterone propionate in the dose of 25 mg. per day intramuscularly for 5 days was given in addition to fluids, and newer chemotherapeutic agents. They found that within a few hours of administration, urine flow began and the blood urea fell gradually to normal levels. There were 5 deaths, a mortality rate of 18.5 per cent, which they felt was significantly lower than that for similar patients not treated with the androgen. An actual control series was not established, however.

Since that time, Dérot & Bernier (98) have reported on the treatment with 80 mg. of testosterone acetate daily of four patients with anuric nephritis. All four patients survived, but the authors do not ascribe all of the success to the androgen since other treatment, including peritoneal dialysis in two patients, was used. Fabre (99), observing that his surgical operations were followed by oliguria which could be prevented by testosterone, advocated the routine administration of androgen both before and after each operation. These are fragmentary reports which must be confirmed by a larger, more controlled experience.

Discussion

What then can be the value of hormonal medication in human renal disease? Both experimental and clinical experience has shown that it is of little value in established parenchymal renal disease. In fact, renal *function* (as opposed to anatomic renal changes) can be little influenced by androgens in the normal kidney, and treatment is further hampered by the clinically demonstrable "wearing off" effect, which renders the compound impotent [illegible] the case is [illegible] of the disease. The same should be true of the prevention as opposed to the treatment of anuria, administration of androgen on the day of the renal insult might affect the development of lower nephron nephrosis with its severe tubular changes.

Hydronephrosis may be an exception. Repair after release of obstruction occurs in islands of better blood supply. Homburger's evidence is that repair nodules are increased with certain androgens Perhaps renal counterbalance, which works against repair in the weaker of two kidneys, could be held in abeyance by androgen therapy until the damaged nephron had so repaired itself that it could compete with the normal one. At the present writing, this is pure conjecture. We must conclude that at the moment, the renotrophic effect of androgens has experimental but no clinical value.

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DISEASES OF THE RETICULOENDOTHELIAL SYSTEM AND HAEMATOLOGY[1]

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Introduction

It is impossible in this review to survey more than a fraction of the publications provided by research and observation in haematology during 1951 and 1952. Contributions to the problems of blood coagulation, immunology and blood groups, the genetic anaemias and several other major fields have reluctantly been excluded, and attention confined to certain common anaemias and their related metabolic problems, purpuric states, leukaemia, the use of ACTH (corticotropin) and cortisone, endocrine influences on the blood, the reticuloses, plasma cell and serum protein disorders, and some toxic drug effects on the blood.

Anaemias

Iron metabolism and iron deficiency anaemias.—The studies of Huff *et al.* (1) have continued to throw light on problems of "ferrokinetics." These authors observed the movement of intravenously injected Fe^{59} in tracer doses by external scintillation counting over bone marrow, liver and spleen, and by *in vitro* analysis of plasma and red cell radioactivity in seven normal subjects and in 30 patients with various erythropoietic disorders A uniform kinetic pattern occurred in normal young adult males, with initial major transient accumulation at constant velocity in the bone marrow, and minor initial accumulation in the liver. The bone marrow discharged to newly formed erythrocytes which entered the circulation, and the liver discharged to the major pathway. Abnormalities in initial direction, destination, and velocity of transport were encountered in patients and these are described in some detail. No firm generalisations can yet be made, but the work clearly demonstrates the potential value of such studies in elucidating haemopoietic disorders and perhaps as a future guide to therapy. The fate of the injected Fe^{59} tracer was followed for only 15 days, and comparison with earlier animal experiments suggests that a longer period of follow-up would be advisable (2).

Wasserman *et al.* (3) have devised a method for measuring the rate of removal of radioactive iron from the plasma. The rate is decreased in marrow aplasia and when iron stores are increased as in haemosiderosis, while conditions with enhanced erythropoietic activity are associated with an increased rate of loss of plasma iron. The authors suggest that the halftime of plasma radioiron disappearance when body iron stores are normal is a sensitive measure of the integrity of the erythropoietic tissues. Normal levels of

[1] The survey of literature pertaining to this review was concluded in July, 1952.

plasma iron in 130 subjects were found to range from 20 to 265 μg. per 100 ml. blood, and no significant differences from normal were observed in patients with achlorhydria [Fowler & Barer (4)]. These workers did not encounter diagnostic changes in plasma iron in a number of blood dyscrasias. Klopper & Ventura (5) describe a characteristic pattern of low serum iron, considerably increased iron-binding capacity of serum protein and low serum copper, with an increase in free erythrocyte protoporphyrin in true iron deficiency. Search for this pattern should facilitate the difficult assessment of iron deficiency states in late pregnancy. In 19 patients with neoplasms unaccompanied by haemorrhage, the serum iron levels were below normal and the serum copper increased [Pirrie (6)]. The inverse correlation of these values was significant, and the author suggests that a depression of haemoglobin synthesis reduces the demand for catalytic copper. Serum iron studies are of diagnostic value in haemochromatosis since all of seven patients with this disease had high fasting serum iron levels, complete saturation of serum iron-binding capacity and flattened iron absorption curves [Houston & Thompson (7)].

Hypochromic iron deficiency anaemia in young adult males is not common, but Shorthouse & King (8) record 20 cases in young servicemen in which there was no evidence of blood loss. Most showed definite immaturity and some nail changes, but the typical features of this type of anaemia, as seen in older women, were not encountered. The blood pictures mostly returned fully to normal with oral iron. The authors suggest that during early adaptation to service life there may have been an increased demand for iron coupled with defective intestinal absorption. Gram & Leverton (9) compared the absorption of three different iron salts in normal women. No real differences in uptake were found between ferrous gluconate, lactate, and sulphate.

Preparations of iron for intravenous use have now been commonly employed for some years, but further reports on their value continue to appear. Holly (10) found minimal toxic effects and good therapeutic response to intravenous saccharated iron oxide in iron deficiency states in obstetric and gynaecological practice, and Lucas & Hagedorn (11) obtained good results with a high molecular ferric carbohydrate compound.

The attractive appearance of some varieties of ferrous sulphate tablets has led to several serious cases of poisoning in children and probably many minor unreported incidents The clinical picture of such poisoning and accounts of the 17 cases at present reported, including eight fatal cases, have been reviewed by Spencer (12).

Megaloblastic anaemias and factors which influence them.—The interrelationships of the B_{12} group of vitamins, folic acid, the citrovorum factor, and other substances which influence the megaloblastic anaemias are still obscure. Girdwood (13), in an excellent review, has surveyed a multitude of published observations and discussed the possible interpretations, but no acceptable pattern fitting all the experimental data has yet been discovered. Further review articles have helped to clarify the situation with regard to

Vitamin B_{12} [Lederer & Prinzie (14)], the mechanism of action of folic acid and vitamin B_{12} in the treatment of megaloblastic anaemias [Gajdos (15)], and the relationship of folic acid to the citrovorum factor and B_{12} [Welch & Heinle (16)]. Jacobson & Good (17) describe experiments which show that folic acid, when treated with xanthine oxidase, is partially converted into a substance (perhaps to folinic acid) with greater haemopoietic activity in pernicious anaemia while Spray & Witts (18) have studied the conversion of folic acid to the citrovorum factor in health and pernicious anaemia. These authors gave test doses of pteroylglutamic acid to normal individuals, and to treated and untreated pernicious anaemia cases. Untreated pernicious anaemia patients excreted less folic acid after the test dose than did the other groups, and while all three groups showed increased citrovorum factor excretion after the test dose of folic acid, the increase was greater in normals and treated pernicious anaemia patients than in pernicious anaemia in relapse. In relapse there may be deficient conversion of folic acid to citrovorum factor or increased tissue avidity for the citrovorum factor.

Several more publications report the results of further *in vitro* studies of the megaloblast-normoblast relationship. Callender & Lajtha (19) have suggested a tentative scheme in expansion of Castle's hypothesis. They conclude from *in vitro* experiments that normal gastric juice and vitamin B_{12} together form a thermolabile haemopoietic factor which will ripen megaloblasts to normoblasts, while neither gastric juice nor B_{12} is active alone. The haemopoietic factor in normal serum which converts megaloblasts to normoblasts *in vitro* appears also to be thermolabile, since heating to 56°C. for 2 hr. destroyed some of its activity. The existence of an extragastric as well as a gastric source of intrinsic factor is postulated. Franco & Arkun (20) studied the *in vitro* transformation of megaloblastic marrow under the influence of various substances with the following results. Megaloblasts in normal plasma ripened into normoblasts, but when aminopterin was added the culture remained megaloblastic. Megaloblasts grown in pernicious anaemia plasma remained megaloblastic when vitamin B_{12} was added, developed into intermediate erythroblasts when folic acid was present, and became exaggeratedly megaloblastic when aminopterin was added. They suggest that in pernicious anaemia synthesis of folic acid is replaced by synthesis of folic acid antagonists, and that vitamin B_{12} normally undergoes some change before becoming active haemopoietically Experiments which demonstrate the *in vitro* reversibility between normoblastic and megaloblastic cell series, when cultured in appropriate normal or pernicious anaemia sera, were described in a further paper by Lajtha (21), in which the author also gave technical details of the method if *in vitro* culture be used. Maturation of megaloblasts to normoblasts under the influence of folic acid and the inactivity in this respect of vitamin B_{12} liver extracts, and thymine were reported by Thompson (22). Previous experimental observations of Lajtha, which led him to postulate the existence of a toxic or inhibitory factor in the serum of patients with pernicious anaemia in relapse, could not be confirmed

by Feinmann *et al.* (23) who found no evidence to support the existence of such a factor.

The various natural sources of vitamin B_{12} and its availability from these sources has been a subject of interest, particularly to Hausmann & Mulli (24), and cobalt-containing red pigments with microbiologically active B_{12} have been obtained from animal dungs, beef muscle, and various bacterial cultures. The vitamin from these sources became therapeutically active only after digestion with hog stomach or pancreatic enzymes, but these authors have now described another such pigment obtained from autoclaved fish. In this case conversion into clinically active B_{12} could be performed by treating with potassium cyanide. It is suggested that the inactive pigments may be peptide conjugates of B_{12} and that cyanide releases B_{12} from the peptide link. The subject is briefly reviewed in a *Lancet* editorial article (25).

The vitamin B_{12} concentrations of seurm and urine of normals and of patients with various anaemias were assayed using *Euglena gracilis* as the test organisms [Mollin & Ross (26)] Pernicious anaemia and other megaloblastic anaemias which responded to B_{12} showed much lower serum B_{12} concentrations and lower urinary excretion than did normals and patients with other diseases. On the other hand Sokoloff *et al.* (27) found no significant differences in urinary excretion of vitamin B_{12} in pernicious anaemia patients and others initially or after various doses of B_{12}. The test organism in these experiments was Lactobacillus *leichmanii*

Cartwright *et al.* (28) attempted to produce dietary deficiency of vitamin B_{12} in swine, but were unable to provoke a macrocytic anaemia or megaloblastic marrow. These results contrast sharply with the ease of production of folic acid-deficiency anaemia with macronormoblastosis. While the deficiency may not have been severe enough, the authors feel that folic acid may prevent the development of macrocytic anaemia even in the absence of vitamin B_{12}

The formation of a small intestinal cul-de-sac in the rat leads to macrocytic anaemic in a proportion of cases, provided the cul-de-sac has stagnant contents and is placed in the upper part of the small intestine [Watson & Witts (29)] The anaemia is sometimes associated with steatorrhoea and with haemolysis and responds well to folic acid or aureomycin but poorly, or not at all, to vitamin B_{12}. An interesting clinical parallel to these experiments is provided by the case of Dvoskin *et al.* (30) in which a patient with severe refractory anemia was cured by resection of a blind loop of intestine

Clinical reports of megaloblastic anaemias have been numerous. A plea for exact diagnosis before multiple therapy is given has been put forward once more [Heck (31)] Evidence is provided of the existence of frequent folic acid deficiency in mothers and children [Spies *et al.* (32)]. A further case of megaloblastic anaemia of infancy has been reported, response to folic acid therapy was dramatic [Rickards (33)]. The effects of combined folic acid and liver extract therapy in pernicious anaemia are not more satisfactory than with liver extract or B_{12} alone and combined therapy did not produce

any suggestion of subacute combined degeneration of the cord [Chodos & Ross (34)]. Although many reports of megaloblastic anaemia of pregnancy failing to respond to vitamin B_{12} have appeared in the past, Chaudhuri (35) described 16 cases which all responded satisfactorily to a daily dose of 4 to 11 μg Vitamin B_{12} concentrates derived from mould cultures may give rise to skin idiosyncrasy [Bedford (36)], and this was the case in 14 of 100 people tested. The sensitivity is due not to the vitamin B_{12}, but to impurities carried over from the mould fermentation liquor. The response of some megaloblastic anaemias to intramuscular penicillin, previously reported, has now been shown to occur also with oral penicillin [Foy *et al.* (37)]. The frequency of latent idiopathic steatorrhoea as a cause of megaloblastic anaemia in the young adult is stressed by Conway (38). Two curious developments in cases of pernicious anaemia were reported; the presence in two patients with pernicious anaemia and infections of a leukaemoid bone marrow resembling myeloid leukaemia, but responding fully to vitamin B_{12} and returning to normal [Strauss *et al.* (39)], and the curious progression from pernicious anaemia in relapse to remission under Vitamin B_{12} and onwards to polycythaemia vera [Galt *et al.* (40)].

In a fine cytological study of the megaloblast-normoblast problem, which will be most valuable to haematologists, Downey (41) discusses, among other things, the difficult problem of the "intermediate erythroblast."

Haemolytic anaemias.—The occurrence of viremia in acute haemolytic anaemia and in autohaemagglutination has been demonstrated by Moolten & Clark (42) in one of the year's most stimulating reports In their initial case, the virus was that of Newcastle disease, and a preliminary survey carried out by these workers indicates that multiplication of latent viruses may be the cause of haemolytic anaemia in Hodgkin's disease, leukaemia, lymphosarcoma, and other disorders of the reticuloendothelial system A positive Coombs' test may be due to adsorption of antiviral antibodies on virus-sensitized red cells and not to a haemolytic autoantibody. When the Coombs' test is negative a positive antialbumen test may be found when serum albumen has perhaps been adsorbed on the red cell as a result of viral injury. If the Coombs' reagent has been prepared by immunising rabbits with whole blood serum instead of with the globulin fraction alone, false positive tests may be expected. The authors conclude that viruses should be sought in clinical conditions complicated by haemolytic or haemagglutinative phenomena.

Immunological problems in relation to diagnosis and treatment of acquired haemolytic anaemia have been reviewed by Eyquem (43), Dameshek (44), and Dacie (45). The difficulty of foretelling from haematological or clinical observation the possible response to transfusion, exsanguino-transfusion, or splenectomy has been emphasized by Dreyfus *et al.* (46) in a study of 12 cases with auto-antibodies. Dacie & de Gruchy (47) investigated a series of patients with acquired haemolytic anaemia for the presence in their sera of abnormal antibodies active against red cells Nonspecific antibodies were

found in 19 cases of idiopathic acquired haemolytic anaemia, haemolysis following virus pneumonia or chronic haemolytic anaemia with haemoglobinuria and Raynaud's phenomenon. Trypsinised normal red cells and paroxysmal nocturnal haemoglobinuria red cells were found to be valuable reagents for the detection of haemolytic antibodies; they enabled the demonstration of "warm" or "cold" haemolysins in the sera of 13 of the 19 patients. In three patients who responded clinically to splenectomy the antibody titre did not change. The authors feel that haemolytic antibodies probably play some part in the production of haemolysis *in vivo*. Zinkham & Diamond (48) have studied another factor in the haemolytic process, and found that marked erythrophagocytosis occurred *in vitro* when the buffy coats of three patients with acquired haemolytic anaemia were incubated at 37°C. for 1 hr. The patients all had positive direct and indirect Coombs' tests and increased red cell mechanical fragility. A fourth similar patient did not show erythrophagocytosis

Blood disorders and, in particular, haemolysis have been experimentally produced by injection of antierythroblastic, antileukoblastic, and antimegakaryocytic sera [Bracco *et al.* (49)]. The first antiserum produced marrow hypoplasia and peripheral haemolysis, while the two latter sera provoked a moderate haemolytic anaemia, peripheral agranulocytosis, and bone marrow granulocytic hypoplasia. Reticulocytes and young red cells in dogs have been shown to be two to four times as resistant to haemolytic serum as normal red cells, an observation which throws light on the very high reticulocytosis of some cases of haemolytic icterus [Cruz & Junqueira (50)]. In patients with jaundice of hepatic or obstructive origin, 17 out of 18 showed decreased saline red cell fragility. The degree of decrease tended to parallel the intensity of the jaundice [Movitt *et al.* (51)].

Observations made by Berlin (52) indicate the presence of increased blood destruction during 6 to 10 days preceding the onset of menstruation. The hyperhaemolysis was followed by reticulocytosis A similar curve was found in a splenectomised woman, and hormonal influences are probably responsible.

A considerable number of instructive case reports have been published. Willcox (53) recorded four cases of haemolytic anaemia, two with positive and two with negative Coombs' tests, in association with reticuloses: Hodgkin's disease, histiocytic medullary reticulosis, lymphosarcoma, and reticulum cell sarcoma The possible mechanisms of haemolysis were discussed but no definite conclusions could be drawn and the question of viraemia was not raised. Acute haemolytic anaemia associated with myeloid metaplasia of the spleen was greatly improved by splenectomy [Claman & Collier (54)], and a symptomatic haemolytic anaemia in a child with an ovarian teratoma was cured by excision of the tumour [Allibone & Collins (55)]. A patient with hepatic cirrhosis and haemolytic anaemia had incomplete "cold" antibodies [van Loghem *et al.* (56)]. Acquired acute haemolysis with autoantibodies in a child of seven weeks was accompanied by thrombo-

cytopenic purpura which may have been due partly to antibody action [Gasser & Holländer (57)]. Aaron (58) found a high cold agglutinin titre in a case of viral pneumonia with haemolytic anaemia. Acute idiopathic paroxysmal cold haemoglobinuria of nonsyphilitic type in a child of three and a half years was reported by Sweetnam *et al.* (59). An unusual case, thought to be paroxysmal nocturnal haemoglobinuria in type, in which haemolysis could be provoked by prolonged exposure to cold, was described by Crosby & Bell (60), who also demonstrated that the increased haemolysis in nocturnal haemoglobinuria on lowering pH was not due to increase in pressure of carbon dioxide. The association of disseminated lupus erythematosus and acute haemolytic anaemia, both improved by cortisone, was reported by Pisciotta *et al.* (61).

The effects of ACTH and cortisone in treatment of haemolytic anaemia have been the subject of several reports, and these are reviewed in a later section.

A review of erythroblastotic disease of infants and blood group studies is omitted from lack of space, but a preliminary report on controlled trials of the treatment of haemolytic disease of the newborn, carried out at several centres in England, warrants inclusion because of its great general interest [Mollison & Walker (62)] These studies on 477 infants showed that the practice of inducing labour three to five weeks before term was associated with a scarcely significant lowering of the proportion of surviving infants, while exchange transfusion was followed by a significantly higher survival rate than was simple transfusion.

Platelets and Purpura

A thrombocytopenic factor has been demonstrated in the blood of patients with thrombocytopenic purpura by Harrington *et al.* (63) The factor was present in the blood or plasma of 8 of 10 patients with idiopathic thrombocytopenia and one of three with secondary thrombocytopenia The injection intravenously of 500 ml of citrated whole blood from these nine patients led to prompt and dramatic falls in the platelet counts of normal recipients. The effect lasted five to seven days and was sometimes severe, with prolonged bleeding time, decreased prothrombin consumption, and even gross gastrointestinal haemorrhage The factor was stable for 9 days at 5°C. and 8 days at 25°C. It was present in the globulin fraction of plasma. After splenectomy the factor was still present, but was probably reduced in one case after cortisone administration The studies of Hirsch & Gardner (64) on the life span of transfused human platelets showed that the platelets survived only 24 hr. when the recipient was suffering from acute thrombocytopenic purpura, while surviving 4 to 8 days in chronic thrombocytopenia, and 4 to 6 days in aplastic anaemia and leukaemia The humoral factors at work in thrombocytopenia have been considered by Evans *et al* (65) as comparable to those operating in haemolytic anaemia, and a spectrum-like relationship is postulated between these diseases. The conditions may be present

simultaneously and some cases of idiopathic thrombocytopenic purpura with no haemolysis have a positive Coombs' test and may show a platelet agglutinating antibody. Stefanini & Silverberg (66) have demonstrated that when saline-washed platelets are added to the serum of haemophiliac, thrombocytopenic, or healthy persons, agglutination occurs if prothrombin activity is sufficient. The agglutination is directly proportional to the prothrombin activity in the serum, and is accompanied by evolution of thrombin. These authors give warning that in platelet agglutination studies designed to seek for immunological or destructive mechanisms, the sera must be thoroughly deprothrombinized before use, or false positive reactions may occur. The agglutination and destruction *in vitro* of normal platelets by the serum of a patient with acute thrombocytopenic purpura has been reported by Dausset *et al.* (67), who showed that this serum inhibited normal clot retraction Studies on the effect of transfusion of platelet-rich polycythaemic blood on the platelets and haemostatic function in idiopathic and secondary thrombocytopenic purpura, have shown disappearance of injected platelets from the circulation of patients with idiopathic thrombocytopenia within 30 min. to 12 hr. This observation by Stefanini *et al.* (68), suggests a humoral destructive mechanism not present in secondary, amegakaryocytic cases, where platelet survival was 48 to 96 hr. The humoral factor does not appear to originate in the spleen, but may inhibit platelet production from bone marrow megakaryocytes. Long-lasting or permanent remissions have occurred after transfusion of polycythaemic blood, and this perhaps contains a platelet stimulating factor. In further studies on platelets, Stefanini *et al.* (69, 70) demonstrated the absence of selective sequestration and destruction of platelets by the spleen in idiopathic thrombocytopenic purpura, and the absence of any major platelet removal mechanism in the lungs in this disease.

In addition to the platelet accelerators previously shown to be active at two stages of the clotting reaction, a third platelet factor has been demonstrated which can neutralize heparin [van Creveld & Paulssen (71)] The factor has been shown to be a phosphatide and to be necessary for the full action of antihaemophilic factor of normal plasma [van Creveld & Paulssen (72)]

A review of vascular factors in the pathogenesis of haemorrhagic syndromes by Spaet (73), provides a good source of references to work on this subject. In rats rendered purpuric by an antiplatelet serum parenteral rutin diminished the purpura and improved capillary resistance, but did not affect the bleeding time or platelet count [Witte & Wilmes (74)]. Jackson *et al.* (75) could find no evidence of a circulating anticoagulant in postirradiation purpura in dogs, and think the haemorrhagic and clotting defects are a result of thrombocytopenia rather than hyperheparinemia, as had [illegible] suggested.

Among other studies of purpuric states and [illegible] be mentioned an excellent assessment of the [illegible]

nations [O'Brien (76)], some simple methods of measuring platelet adhesiveness [Rovatti (77)], and a report of increased marrow megakaryocytic activity at the tenth postoperative day [Kerhulas *et al.* (78)].

Case reports of thrombopathic conditions have been numerous and include a further report on thrombotic thrombopenic purpura by Blackman *et al.* (79), two cases of Willebrand-Jurgens thrombopathy providing evidence for the idea of qualitative platelet abnormality as the basic defect in

successful and the foetus stillborn, but despite the thrombocytopenia there was no excessive blood loss at delivery.

The sharp differentiation between acute and chronic idiopathic thrombocytopenic purpura has been emphasized by Hirsch & Dameshek (83) in an analysis of 89 cases. The authors describe a number of distinguishing features which are of great importance since the acute cases are likely to recover spontaneously in three to four months and splenectomy is usually unnecessary, while chronic cases do not lose their thrombocytopenia spontaneously, though they frequently respond to splenectomy.

Leukaemia

Studies on the aetiology and nature of leukaemia prior to the period covered by this review have been discussed and analysed by Furth (84), who concludes that leukaemic cells are essentially neoplastic. The evidence is fairly reviewed, although the contribution of *in vitro* culture studies is rather briefly dealt with, and, as, Furth points out, his conclusion is very much a matter of opinion The role of virus in the production of leucotic change has been emphasized during the last year in several papers. Gross (85) demonstrated the pathogenic properties of a mouse leukaemia agent which could be vertically transmitted through several generations. Mas y Magro (86, 87) reported the experimental heterologous transmission of acute human myeloid leukaemia to guinea pigs on three occasions, and subsequent repeated transmission homologously in guinea pigs. All the inoculated animals died, and developed before death a "leukaemic" blood count, with neutrophilia and presence of atypical promyelocytes Torrioli & Torrioli (88) recapitulated work done during the last ten years and published previously in Italian journals, which supports the concept of a virus aetiology in leukaemia. Human leukaemic blood inoculated into chick embryos led to reticuloendothelial changes in 40 per cent. These mesenchymal hyperplastic changes could be transmitted to other embryos and material from diseased chick embryos injected subcutaneously in leukaemic patients produced nodular reactions, while normal chick embryo material produced no such reaction. Shay *et al.* (89) succeeded in inducing myeloid leukaemia in rats by gastric instillation of methylcholanthrene, and achieved a high percentage transfer by intraperitoneal injection of peripheral blood from leukaemic rats to very

young normal animals. In a later paper, Gross *et al.* (90) described spherical particles 20 to 200 mμ in diameter obtained from all of 72 filtered leukaemic spleen, liver, and gland extracts in mice. The authors present some evidence of leukaemia transmission achieved with these particles.

The role of the lungs in the removal of transfused lymphocytes in rats [Weisberger *et al.* (91)], supports earlier suggestions that the level of leucocytes may be partly controlled by a pulmonary mechanism. Bierman *et al* (92, 93), who had previously done much pioneer work on this possible mechanism, have discussed the function of the pulmonary circulation as a source of leucocytes and platelets in man and have shown that the lung leucocyte-removing mechanism operates on indigenous white cells as well as on infused foreign cells.

Data on average cell size for various types of leukaemia are needed to allow volume computations from leucocyte counts in chemical and radioactivity investigations on small amounts of blood. This information has been made available by Tivey *et al.* (94).

Davidson and co-workers (95) have provided quantitative support for cytochemical observations that primitive cells from bone marrow or leukaemic blood contain more ribonucleic acid than do mature cells. A method for viscosimetric determination of desoxyribocunlease activity and of desoxyribonuclease inhibitors has been described by Henstell & Freedman (96). By the use of this method Henstell *et al.* (97) have shown a direct relationship to exist between the degree of cellular maturity of normal and leukaemic blood and bone marrow white cells and their desoxyribonuclease inhibitory activity. The most mature white cells of blood contain a maximum and the primitive "blast" cells of leukaemia a minimum of inhibitor.

Some interesting observations on granulocytolysis *in vitro* in myeloid leukaemia have been reported [Aleksandrowicz & Miklaszewska (98)]. These experiments show that plasma in acute myeloblastic leukaemia contains a factor which accelerates the disintegration of white cells in the peripheral blood, while plasma in chronic myeloid leukaemia contains a factor which slows down white cell disintegration. Normal plasma possesses a white cell-destroying factor only half as active as that of acute leukaemia, but three times as active as the chronic leukaemia factor.

The pathogenesis of bleeding in leukaemia has been a subject of much interest in recent years, and Freeman (99) has shown that bleeding in leukaemia in the presence of massive infections may be partly due to anticoagulant bacterial polysaccharides Polysaccharides derived from cultures of *Bact. friedländeri* and *Serratia marcescens* prolonged the coagulation time of diluted plasma *in vitro*, an effect which appeared to be exaggerated in thrombocytopenic leukaemia serum. Freeman & Hyde (100) have also studied the roles of prothrombin activity, heparin-protamine titre, and platelet concentration in bleeding of leukaemia. They assayed heparin and heparin-like anticoagulants neutralizable by protamine in children with

acute leukaemia. Bleeding occurred with equal frequency among those with normal and those with elevated heparin-protamine titres. When protamine titres were calculated on the basis of unit plasma volume, identical medians and similar distributions were found for both bleeding and nonbleeding leukaemic cases. The bleeding did not appear to be dependent on coagulation defects demonstrable by prothrombin time. The regular association of platelet levels below 50,000 or 60,000 per C. mm. with bleeding in acute leukaemia was reaffirmed.

Among a number of interesting surveys of ecological and genetic problems of leukaemia are those of Bernhard *et al.* (101) on congenital leukaemia, Dausset & Schwarzman (102) on the influence of age and sex upon frequency and cytological types of human leukaemia, and Dausset (103) on the apparent antagonism between lymphoid and myeloid leukaemias and its relationship to endocrine factors. It is curious to note that of the 18 cases of congenital leukaemia accepted as authentic by Bernhard, 17 were granulocytic, while, as Dausset emphasises, childhood leukaemia is most often lymphoblastic. Anderson (104) has reported the incidence of leukaemia in five siblings and reviewed the genetic aspects of this disease. He concludes that a rare recessive gene with high penetrance may be involved in familial cases. A comprehensive analysis of the incidence, distribution, and fatality of myelocytic leukaemia between the years 1910 to 1948 has been published [Shimkin *et al.* (105)]. Many reports of leukaemic patients with unusual complications have appeared. A normal healthy infant was born of a mother whose pregnancy was complicated by monocytic leukaemia and pulmonary tuberculosis [Beven (106)] A patient with hypersplenism, apparently cured by splenectomy, developed lymphatic leukaemia 18 months later [Cochrane & Gross (107)]. Scutt (108) has reviewed the occurrence of bullous skin lesions in chronic lymphatic leukaemia and reported a further case of this unusual finding Two cases of acute leukaemia with hypocellular marrow were encountered by Beyers *et al.* (109). Mallarme & Bourel (110) have discussed the erythroblastic onset of malignant leucoses and the relationship of these disorders to the acute erythroblastosis of Di Guglielmo. Rachet and associates (111) have recorded a case of erythroleucomyelosis with purely erythroblastic onset, and Verloop *et al.* (112) illustrate with a case report, the variations in the clinical picture of erythroblastosis and leukaemia Polychromatic normoblastic erythraemic myelosis in a girl aged 13 has been described by Emery (113) while Sarrailhe (114) has reported a further case of acute erythroblastosis. This disease continues to be reported much more often from the continent of Europe than from elsewhere Two cases of acute leukaemia showing severe hypokalemia led Videbaek (115) to suggest that sudden death in acute leukaemia may sometimes be due to potassium deficiency.

A patient with acute leukaemia had four spontaneous complete remissions, each preceded by a leukopenic agranulocytic hypoplastic phase in

blood and marrow [Bassen & Kohn (116)]. The authors believe that therapeutically induced remissions probably follow a similar pattern. The possibility that idiopathic aplastic anaemia is only a phase of acute leukaemia, at least in children, is discussed.

No very striking advances have been made in the treatment of leukaemia, but reports on the use of antimitotic drugs, ACTH, and suprarenal cortical hormones continue to accumulate. Bessis *et al.* (117) found nitrogen mustard, urethane, formol, and Phenergan [10-(2-dimethylamino-1-propyl) phenothiazine] to be without effect on the development of transmissible erythroblastosis of fowls, but two folic acid antagonists exhibited a clear preventive action. The effect of colloidal Au^{198} on the growth cycle of leukaemic cells and on host survival in mice has been studied by Goldie *et al.* (118). The radioactive gold exerted a direct cytotoxic action on leukaemic cells, improved the cell regulatory mechanisms of the host and stimulated the reticuloendothelial system. A synergistic action was exerted with aminopterin. Abu Jamra & Gomide (119) performed elaborate balance experiments on nitrogen metabolism and 17 ketosteroid excretion in cases of leukaemia treated with urethane, but found no real evidence of a general increase in cellular catabolism though leucopenia was regularly produced. The results of a careful study over several years of the value of nitrogen mustard therapy in leukaemia have now been published by Gardikas & Wilkinson (120). They treated 102 patients who were followed up for several years. In acute leukaemias results were completely disappointing, but in chronic leukaemias a careful comparison with data from the literature justifies the conclusion that the results are as good as the best obtained with x-radiation or radioactive phosphorus. Toxic effects were not severe.

The action of folic acid antagonists and their clinical application has been the subject of a short review by Dresner & White (121), and the *Proceedings of the Second Conference on Folic Acid Antagonists in the treatment of leukaemia* (122) provide a general discussion of work and experiences on this subject which amounts to an extensive review of the present status of these drugs The clinical responses of different types of leukaemia to folic acid antagonists are now well known, but further figures have been given by Wilson (123) in a report on 70 patients Swendseid *et al.* (124) have obtained experimental data which show that during treatment of leukaemia with aminopterin significant amounts of this drug are retained by the body for a considerable period, while the excretion of folic acid itself is increased These findings are in accord with the theory that aminopterin metabolically displaces folic acid, a concept which would also explain why aminopterin effects are not readily reversible by folic acid Further studies by Swendseid *et al.* (125) on the nutritional status of folic acid in persons with leukaemia, have suggested that the clinical results of aminopterin therapy may depend on the initial degree of folic acid nutritional depletion Such depletion was more frequent and severe in chronic leukaemia, particularly lymphocytic, than in acute leukaemia, and it seems possible that measurement of folic acid excretion

after test doses might enable the subsequent response to aminopterin to be predicted. Combined aminopterin and cortisone therapy in seven cases of acute leukaemia produced good remissions in all, and the combined medication was tolerated better than separate treatment with either drug alone [Marie *et al.* (126)] Bernard & Mathe (127) have also reported excellent results with such a combination of drugs in a further 14 cases. The ultimate prognosis remains hopeless. A high percentage of patients who have developed resistance to hormone or antifolic acid therapy, respond to the other method of treatment [Kingsley Pillers *et al.* (128)]. Cortisone and ACTH have presumably a different primary mode of action on the leukaemic process from that of folic acid antagonists.

Triethylenemelamine appears to have a definite place in the treatment of many neoplastic, leukaemic, and lymphomatous conditions [Rundles & Barton (129); Silverberg & Dameshek (130)]. Particularly good results have been obtained in the chronic leukaemias and in Hodgkin's disease, and in these conditions the drug may perhaps become the agent of choice.

Cortisone and Corticotropin

Rosenthal *et al.* (131) examined the bone marrow of 12 patients with nonhaematological diseases before and during cortisone and ACTH therapy. All showed significant decreases in eosinophils of the peripheral blood, but no change in marrow eosinophilia. Bone marrow cellularity and differential counts did not alter during steroid therapy. In normal guinea pigs, however, daily intraperitoneal injections of ACTH for seven days led to increased marrow cellularity, with particular increase in myeloid and erythroid elements [Hudson *et al.* (132)].

Repeated doses of ACTH and cortisone were followed by increased capillary resistance, while desoxycorticosterone acetate caused a fall and other hormones had no effect. This test, using the negative pressure method for determining capillary resistance, is felt to be a simple and sensitive index of adrenocortical response to stimuli [Robson & Duthie (133)] Itelson (134) calls attention to the distinction between the small and large lymphocyte response to the steroids. ACTH causes an increase in numbers of small lymphocytes, while cortisone influences only neutrophils and large lymphocytes.

An investigation panel of the Medical Research Council in England has published a preliminary report on the treatment of blood disorders with ACTH and cortisone (135). The report concerns 88 patients. Remissions occurred in a proportion of cases of acquired haemolytic anaemia and of thrombocytopenic purpura, but results were uncertain and unpredictable No effects were produced in aplastic and refractory anaemias Of 36 cases of acute leukaemia, one complete and eight partial remissions occurred The effects were temporary Wintrobe *et al* (136) have amplified their earlier reports and now discuss the results obtained in 40 cases of blood disorders of various sorts. While the findings are too elaborate to abbreviate, the gen-

eral conclusion seems warranted that the hormones are chiefly of value in acquired haemolytic anaemia and in idiopathic thrombocytopenic purpura. Most individual reports of successful therapy support these two surveys. Andre & Dreyfus (137) found general clinical improvement but no haematological remissions in nine cases of adult leukaemia, five acute and four chronic. Jacobson & Sohier (138) treated three cases of idiopathic thrombocytopenic purpura with the production of short remissions when platelets rose to normal or high levels. Relapse followed cessation of therapy after one to eight weeks. Evans & Liu (139) record a good remission with ACTH in a case of chronic severe primary thrombocytopenic purpura. A more extensive series of purpuric cases was studied by Stefanini *et al.* (140), who treated 15 patients with acute or chronic idiopathic thrombocytopenia without producing any permanent remissions. Nevertheless, ACTH and cortisone appeared to reduce spontaneous bleeding, improve capillary fragility, and shorten bleeding times. These authors recommend that the steroid hormones should be used to control severe bleeding particularly in acute cases which will probably remit spontaneously, prior to splenectomy to reduce blood loss at operation, and to control bleeding after unsuccessful splenectomy.

Good results in acquired haemolytic anaemia were obtained by Best *et al.* (141) and by Christol *et al.* (142) with ACTH or cortisone, while Rosenthal and co-workers (143) treated four patients with acquired haemolytic anaemia and circulating antibodies with compound F acetate. Two patients given compound F intramuscularly responded only partially though ACTH, and cortisone in these two patients later produced good remissions. Oral therapy with compound F in two other patients led to one complete remission and a partial remission in the other patient, who later responded fully to cortisone. The authors feel that further study of compound F in acquired haemolytic anaemia is called for. Agranulocytosis has been successfully treated with ACTH [McMillin (144); Dudley Hart *et al.* (145)].

Endocrine Influences and the Blood

A lengthy review of disorders of the red cells in endocrine disease, and the role of the endocrine glands in erythropoiesis has brought together more than 500 earlier contributions to this subject [Aschkenasy (146)]. Bousser & de Menibus (147, 148) have discussed the conduct of treatment of anaemias in myxoedema, and given their opinion that megaloblastic anaemias in myxoedema are coincidental. Macrocytic anaemia with normoblastic marrow may occur and respond to thyroid. The anaemia of hypopituitarism has been the subject of a report by Summers (149). This author describes two types of anaemia encountered in 10 cases, macrocytic hypochromic and normocytic hypochromic. Thyroid, testosterone, and iron were unsatisfactory therapeutically, but cortisone produced a prompt improvement.

Scudamore *et al.* (150) have studied erythrocyte and plasma cholinesterase activity in dyscrasias of the blood. Normal values were determined in 20 individuals. Low erythrocyte cholinesterase activity was found in per-

nicious anaemia and hypoplastic anaemia, and high activity in anaemia secondary to haemorrhage and in pernicious anaemia and nutritional macrocytic anaemia in early remission. Plasma cholinesterase in blood dyscrasias was related in general to the albumin concentration, and usually reflected the general clinical state.

Studies of circulating eosinophils, lymphocytes, and neutrophils in normal, adrenalectomised, and hypophysectomised rats subjected to artificially elevated body temperatures were carried out by Hubler *et al* (151). In normal rats a marked eosinopenia and lymphopenia and a considerable neutrophilia occurred. Adrenalectomy abolished the two former changes but did not affect the neutrophilia Hypophysectomy did not greatly alter the response from normal, although the eosinopenia was rather variable. When both adrenal and pituitary glands were excised, the temperature increase did not produce any significant alteration in any of the counts. Removal of adrenal medulla alone allowed a normal response to occur. The authors conclude that hyperpyrexia produces pituitary and cortical stimulation and so affects the leucocytes Hungerford *et al.* (152) found that administration of ACTH was effective in reducing the number of lymphocytes entering the blood stream by way of the thoracic duct. This effect was not duplicated by adrenal cortical hormones in these experiments, and the mechanism of action of ACTH could not be elucidated.

The leucocyte changes following the intramuscular injection of epinephrine hydrochloride have been discussed by Robertson Smith & Hayhoe (153) and Samuels (154), and it is agreed that this response cannot be applied to the diagnosis of hypersplenism without much further study. Complex mechanisms other than splenic contraction are involved.

Endocrine disorders associated with leukaemia, and the effects of treatment of leukaemia with various hormones has been reviewed by Bernard & Bessis (155). Olmer & Gascard (156) have discussed the hypothesis that leukaemia is an adaptation to stress. An extensive review with some 600 references on the relationship of endocrine disturbances and haemorrhagic syndromes has appeared [Croizat *et al.* (157)].

Reticuloses and Neoplasms

Experimental studies on the etiology of Hodgkin's disease have been reported by Bostick & Hanna (158). Lymph node extracts were serially passaged in embryonated chick eggs, and the harvested amniotic fluid was shown to possess virus growth interference activities against Lee influenza virus grown in chick eggs Many tests were performed with the harvested fluid after numerous serial passages, and though most were uninformative, the authors conclude that the fluid possessed "certain filterable, transferable, and virus-like properties." Cells from Hodgkin's disease and leukaemic cells showed about the same degree of cytochrome oxidase activity, demonstrated by the Nadi reaction, as did their normal counterparts [Hoffman *et al.* (159)].

Fadem *et al.* (160) found some evidence of stimulation of bone marrow cell growth by cortisone in Hodgkin's disease, but no beneficial action was observed on the basic mesenchymal disturbance.

Mazar & Straus (161) have provided an interesting review of marital Hodgkin's disease and of the familial and aetiological factors predisposing to it. Lymphocytic leukaemia, with diagnostic marrow findings, has been observed to change into Hodgkin's disease with no post-mortem evidence of leukaemia [Krim *et al.* (162)].

A case of follicular lymphoma of 11 years' duration has been reported in which the clinical, blood, and bone marrow findings were those of acute leukaemia for the first three months of the illness [Anday & Schmitz (163)].

Rubinstein & Smelin (164) have demonstrated the superiority of iliac over sternal marrow aspiration in recovery of neoplastic cells; 100 patients were studied and tumour cells were found in both iliac and sternal aspirates in 15 cases, in iliac alone in 22 cases and in sternal alone in 4 cases The frequency of peripheral erythroblastosis in cancer without anaemia is emphasized by Metzger & Levy (165).

A critical review of hypersplenism with many references has been written by Gelin (166). Chatterjea *et al.* (167) have described a simple technique for splenic puncture, and given splenogram patterns from 43 patients with different blood diseases. The procedure may be very useful in diagnosis of atypical leukaemia, of myeloid metaplasia of the spleen, and of splenic neoplasms.

References to the use of triethylenemelamine have already been discussed and to these may be added the report of Wright *et al.* (168), who treated 42 patients with neoplastic diseases with this drug The best results were in Hodgkin's disease, lymphosarcoma, and chronic leukaemias. There was close correlation between the reaction of the tumour cells in tissue culture to triethylenemelamine and the *in vivo* response. Citrovorum factor corrected the leucopenia which developed during therapy in some cases.

Plasma Cells and Protein Disturbances

One of the most exciting studies reported this year is that of Moeschlin *et al.* (169) on the relationship between plasma cells and antibody formation. Rabbits were sensitized to typhoid vaccine and then given an intravenous injection of the vaccine A plasma cell reaction occurred in the spleen, with plasma cells rising to nearly 50 per cent of the total cell count The peak was at six days Antibodies first rose after five days and their maximum increase was at six to seven days Phase contrast microscopy showed numerous dark granules in the cytoplasm of the plasma cells with greatest incidence on the fifth day. These granulations disappeared as antibodies appeared in the blood and the authors think they are connected with the formation of antibody gamma globulin. ACTH and cortisone given simultaneously with the vaccine injection did not alter the response, but if given eight days previously led to a decreased reaction.

Rundles *et al.* (170) have studied the abnormal serum components of multiple myeloma, and their relation to Bence-Jones protein. By electrophoretic and ultracentrifuge investigations, the average molecular weights of the abnormal serum increments were shown to be about 150,000, and of the Bence-Jones protein about 40,000. The present evidence suggests that Bence-Jones urinary proteins may be derived from the serum increments of higher molecular weight. An unusual case of hyperglobulinaemia was reported by McFarlane *et al.* (171). The serum formed a gel spontaneously on cooling. Electrophoresis showed that normal gamma globulin was absent and alpha and beta globulins much reduced, while an unusual globulin was present in high concentration. The patient showed diffuse infiltration of plasma cells in the marrow, but no areas of nodular plasma cell aggregation. Diffuse myelomatosis may have been the causative condition.

Lawrence & Fortner (172) described a case of acute plasma cell leukaemia without localised bone lesions, in which the peripheral blood was almost aleukaemic and post-mortem examination confirmed the diffuse nature of the marrow infiltrate. Majeranowski (173) reported a similar case, and stressed the distinction from myelomatosis, in particular, the absence of localised bone involvement and hyperproteinaemia.

Luttgens & Bayrd (174) conclude from experience of 66 cases of multiple myeloma treated with urethane over a period of 30 months that this treatment is as good as any at present available. The results are, nevertheless, not very encouraging; about half the patients felt better, but only a fifth showed any objective improvement.

Toxic Blood Reactions to Antibiotics and Other Drugs

Granulocytopenia or agranulocytosis has been reported in association with propylthiouracil [Colwell *et al.* (175)] sulfisoxazole (Gantrisin) [Hagerman & Franzblau (176)], methimazole (Tapazole) [Croke & Berry (177)], and mercurial diuretics [Silverman & Worthen (178)].

Nelson (179) has reported a case of thrombocytopenic purpura and three of pancytopenia complicating arsenotherapy, and the development of thrombopenic purpura due to digitoxin has been observed for the first time [Berger (180)] Purpura and nephritis have been produced by procaine penicillin [Spring (181)], while streptomycin has been incriminated in a further case of thrombopenic purpura [Rudensky & Fisher (182)], and in one case of aplastic anaemia [Sacks *et al.* (183)]

Chloramphenicol has recently been suspected of producing bone marrow depression and blood dyscrasias more frequently than might be thought from published reports. Six cases had earlier been reported and Wilson *et al.* (184) have now added two further aplastic anaemia cases to this list. A nation-wide survey has been started in the United States, and for the present it is recommended that weekly blood counts should be performed on patients taking this antibiotic and that long or repeated courses of treatment should be avoided (185).

Fadem *et al.* (160) found some evidence of stimulation of bone marrow cell growth by cortisone in Hodgkin's disease, but no beneficial action was observed on the basic mesenchymal disturbance.

Mazar & Straus (161) have provided an interesting review of marital Hodgkin's disease and of the familial and aetiological factors predisposing to it. Lymphocytic leukaemia, with diagnostic marrow findings, has been observed to change into Hodgkin's disease with no post-mortem evidence of leukaemia [Krim *et al.* (162)].

A case of follicular lymphoma of 11 years' duration has been reported in which the clinical, blood, and bone marrow findings were those of acute leukaemia for the first three months of the illness [Anday & Schmitz (163)].

Rubinstein & Smelin (164) have demonstrated the superiority of iliac over sternal marrow aspiration in recovery of neoplastic cells; 100 patients were studied and tumour cells were found in both iliac and sternal aspirates in 15 cases, in iliac alone in 22 cases and in sternal alone in 4 cases. The frequency of peripheral erythroblastosis in cancer without anaemia is emphasized by Metzger & Levy (165).

A critical review of hypersplenism with many references has been written by Gelin (166). Chatterjea *et al.* (167) have described a simple technique for splenic puncture, and given splenogram patterns from 43 patients with different blood diseases The procedure may be very useful in diagnosis of atypical leukaemia, of myeloid metaplasia of the spleen, and of splenic neoplasms.

References to the use of triethylenemelamine have already been discussed and to these may be added the report of Wright *et al.* (168), who treated 42 patients with neoplastic diseases with this drug. The best results were in Hodgkin's disease, lymphosarcoma, and chronic leukaemias. There was close correlation between the reaction of the tumour cells in tissue culture to triethylenemelamine and the *in vivo* response. Citrovorum factor corrected the leucopenia which developed during therapy in some cases.

Plasma Cells and Protein Disturbances

One of the most exciting studies reported this year is that of Moeschlin *et al* (169) on the relationship between plasma cells and antibody formation. Rabbits were sensitized to typhoid vaccine and then given an intravenous injection of the vaccine. A plasma cell reaction occurred in the spleen, with plasma cells rising to nearly 50 per cent of the total cell count. The peak was at six days. Antibodies first rose after five days and their maximum increase [illegible] numerous dark [illegible]

and the authors think they are connected with the formation of antibody gamma globulin ACTH and cortisone given simultaneously with the vaccine injection did not alter the response, but if given eight days previously led to a decreased reaction.

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NUTRITION[1,2]

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In selecting subjects for review the writer has been influenced largely by his own special interests or by what would seem to be some of the most outstanding contributions to nutritional science of the year just passed. Naturally much that is of great interest has had to be omitted.

The Nutritional Needs of the Injured

Introduction.—During the last war the metabolic response to physical trauma and the influence of this on nutritional requirements excited considerable interest amongst casualty surgeons and it has stimulated a great many further investigations which have supported the main thesis which the writer has developed over the past twenty years (1 to 8). The importance of all this in relation to nutrition was a sufficient warrant for the National Academy of Sciences and the National Research Council of the United States to publish a report in 1951 on "Therapeutic Nutrition, with Special Reference to Military Situations" (9). More recently, additional information has been provided by Wilkinson and his colleagues (10, 11, 12) and by Moore & Ball (13). From the latters' survey of the literature and from the original investigations they have presented, the clinical picture of the reaction of the patient in varying nutritive and surgical states has been filled in. The National Academy of Sciences and the National Research Council in their Report, and Moore & Ball in their book, use the general nature of the response to draw up detailed guides in aiding the patient to convalescence.

The metabolic response.—It is necessary first to consider the train of reactions which are known to set in when a person is subjected to physical trauma before appreciating the bearing of this on nutritional requirements. It is also of importance to consider the patient's physiological state at the time of the trauma and the relation of this to the sequence of events. Where, for example, the trauma has been produced by surgical intent there has generally been a period of bed rest beforehand and this may of itself have caused some degree of loss of substance through disuse depending on the character of the lesion; further, in this group trauma is induced under general or local anaesthesia. In accidental trauma in civil life the nutritive state of the organism is generally satisfactory but there is no protection from painful stimuli at the time of, and immediately following the injury, apart from that which may result from vasovagal collapse.

In terms of treatment at this stage it is first necessary to make good any

[1] The survey of the literature pertaining to this review was concluded in July, 1952

[2] The following abbreviation was used in this chapter: ACTH (corticotropin)

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with those on nitrogen balance during the six days immediately after major surgical operations Wilkinson *et al.* (10) found that the periods of reduced chloride and sodium excretions coincide often with the increased nitrogen excretion of the catabolic phase. It seems that these retentions are related to the local reaction to injury and the mobilisation to the seat of injury of sodium and chloride from other, undamaged tissues. These observations have raised the question of a re-examination of the soundness of saline therapy at this stage of the illness.

Howard *et al.* (17) found that the output of potassium in man was greatest in the first 24 hr. in fracture cases and Blixenkrone-Møller (18) also found that the greatest amount of potassium was excreted in the first 24 hr. after operation. The Edinburgh workers (11) found that the excretions of potassium and phosphate occurred early in their human postgastrectomy cases and followed a parallel course, as did those of nitrogen and of sulphur which followed later.

The recent work of Pollack & Bookman (19) has shown that the intense negativity of nitrogen balance precipitated by surgical procedures is associated with an excretion of riboflavin many times greater than the ingested amount. In the postoperative convalescent period, as the nitrogen balance is restored and becomes positive, riboflavin retention increases to normal or greater than average normal levels. When a negative nitrogen balance exists because of calorie deficiency or other noninjury response phenomenon there is apparently some loss of ability to retain riboflavin, but there is no excretion in excess of intake. This new evidence supports the theory of an excessive catabolism of body protein and excretion of associated substances. Browne (20) had earlier reported that in burns and fracture cases there may be almost no urinary excretion of ascorbic acid for up to 21 days after injury, despite a daily intake of both orange juice and up to 700 mg. ascorbic acid.

In a review of the relation of vitamin C to adrenocortical function and stress phenomena Pirani (21) finds that in surgical patients urinary excretion of ascorbic acid markedly decreases during the first few postoperative days, while excretion of formaldehydrogenic hormones are several times that of the control period. Plasma level of ascorbic acid is concomitantly decreased. If these patients are given a daily supplement of 1 g. of ascorbic acid, excretion of formaldehydrogenic substances are at a significantly higher level than in the controls and lowering of plasma ascorbic acid is not observed. In this group only 10 to 30 per cent of administered ascorbic acid was recovered in the urine on the day of operation. It has to be remembered that some degree of anuria may then be present. Pirani concludes that stimulation of the adrenal cortex and release of adrenocortical hormones is invariably accompanied by depletion of adrenal ascorbic acid. Increased ascorbic acid utilisation is observed in stress, and this would seem to increase dietary requirement, especially if the stress is severe and associated with extensive tissue injury.

Administration of ACTH[3] but not of cortisone, induces changes in as-

blood loss which jeopardizes the patient's condition. This can be considered a form of nutrition, but the essential action is a restoration of blood volume. The actual protein so administered is apparently only slowly turned over, for the blood proteins do not appear to serve as an immediate source of amino acids for metabolic purposes.

Shortly after moderate to severe accidental injury in man, the writer found that there is, in the previously well-nourished subject, generally a marked loss of nitrogen and sulphur in the urine, reaching their maximal values between the fourth to eighth days. There is also a small rise in temperature, pulse rate, and oxygen consumption.

Cuthbertson, McGirr & Robertson (14) had noted in rats that with the loss of nitrogen there was also a loss of potassium and phosphorus. Analyses of muscle from the injured and uninjured limbs indicated that the loss of potassium was in excess of that of nitrogen. Sodium and preformed creatinine were found to remain relatively constant and a creatinuria also occurred. This wastage of body substance was much greater than would have been accounted for from changes at the site of injury or adjacent to it and appeared to be more of a general bodily response to the exigencies of the repair process.

The picture of the metabolic response to partial operation, in this case gastrectomy, and other surgical operations of similar severity, in well-nourished persons has also been described by Wilkinson *et al.* (12). They noted that an increased urinary nitrogen excretion begins on the second day after operation and lasts from five to eight days, the greatest loss occurring between the second and fifth days. The administration of protein (as such) or of protein hydrolysate intravenously during the period merely increased the urinary nitrogen proportionately and did not modify the "catabolic" phase as described by the writer in any essential way. This increased urinary excretion did not occur in persons who were deprived of food protein but who did not undergo surgical operation.

Wilkinson *et al.* (12) also found that a negative nitrogen balance exists during the postoperative period, irrespective of protein intake, and in persons who receive little or no protein but are not submitted to surgical operation. The postoperative change in protein metabolism is partly a result of the [illegible] and partly of an in- [illegible] The [illegible] early demonstrated by the postoperative increase in urinary nitrogen than by the negative nitrogen balance. In the writer's fracture cases and in those of [illegible] there was little or [illegible] ing operation is simply because of a low intake of protein and energy yielding nutrients (13).

By combining observations on urinary sodium and chloride excretion

creased filtration pressure, unregulated renal salt loss, and a marked intolerance to any sort of additional trauma or infection. Moore & Ball diagnose this type by a maintained high eosinophil count after trauma, continued unregulated sodium loss in the urine, abnormally low urinary excretion of adrenal steroids, and a favourable response to either cortisone or ACTH or both. If the trauma has been massive and there is no overt endocrine disorder it is held reasonable to give cortisone, shifting over gradually to ACTH, tapering this drug off so as to avoid unnecessarily prolonged inhibition of the action of the patient's pituitary.

Immobilization plays only a minor rôle in the metabolic response to injury except in calcium and phosphorus metabolism. Starvation reproduces many of the nitrogen changes seen following trauma and such changes are in part a result of the decreased intake by the ill patient. However, post starvation patients do not reject food or hydrolysate nitrogen as do the post-trauma patients. Starvation produces a very different electrolyte pattern and, apparently, only a sluggish adrenal response As was earlier pointed out by the reviewer (8) ACTH produces a response remarkably similar to the effects of a major operation with the exception that there is less weight loss and an earlier sodium diuresis than after trauma.

The author and his colleagues found that the protein anabolic effect of a crude extract of the anterior pituitary gland could eliminate the nitrogen and creatine loss due to trauma in rats, though it did not appear to have any effect on the healing process. The effect was general rather than local, and possibly represented the normal growth response to this extract, superimposed on and thereby masking the increased catabolism following injury. Certainly no greater rate of restitution of the atrophied muscles of the injured limb was induced; further, the extract had no significant effect on the total time required to heal superficial wounds (24, 25). This experiment demonstrated that the rate of wound healing was not significantly accelerated by a substance which induced an acceleration of general growth, that is, local anabolism was not affected by general anabolism. Further observation on rats fed with dried thyroid gland indicated that an acceleration of metabolism could induce a more rapid healing (26)

Sellers, You & You (27) have reported that thyroid function is not apparently essential for the change in protein metabolism after a burn, while the function of adrenal cortex is an important but not an exclusive factor. The effects of a mild burn and of exposure to cold on urinary nitrogen excretion were found to be cumulative and under the condition of the experiments appeared to be greater than would be expected from the sum of the nitrogen losses due to the two stimuli acting independently (28) The total increase in nitrogen loss by rats after burning and exposure to 1.5°C would be in part because of the combined stress, and partly a result of increased metabolic rate. The results of their studies on thyroidectomized and adrenalectomized animals are held to support the view that different mechanisms are involved in the increased nitrogen loss after burning and after

corbic acid metabolism similar to but less severe than those observed in the injured condition. It has been shown that adrenocortical function is maintained even when the adrenals are markedly depleted of ascorbic acid It seems likely that ascorbic acid can be diverted from other tissues to the adrenals according to need. (The body of the normal adult man has been calculated to contain approximately 4 g. ascorbic acid (22). Of this, probably no more than 1 per cent is contained in the adrenal glands.)

The function of ascorbic acid in the adrenals is fundamentally unknown· it may possibly be concerned with epinephrine stabilisation. Administration of ascorbic acid would seem to be indicated after traumatic injuries and during protracted stimulation of the cortex, as in those exposed to a cold environment.

Moore & Ball (13) also found in their cases that there was a decreased urinary excretion of sodium for two to five days, followed later by a sodium diuresis. A fall in sodium concentration often accompanied the period of positive sodium balance, particularly where trauma was massive. They considered that the drop in circulating eosinophils, which was of a variable order, and the increase in excretion of steroid hormone products, are evidences of an accompanying endocrine readjustment involving the pituitary and adrenal cortex.

It is wise to delay operation on a depleted patient if proper repletion can be carried out preoperatively, provided such a delay does not jeopardize the patient's life If this is impossible, which frequently is the case, then the establishment of a normal intravascular volume with normal concentrations of plasma proteins, crystalloids, and ions must be the essential preliminaries to operation. The earlier the feeding of the patient after operation in such cases, in general the shorter the period of negative balance and the sooner nitrogen retention takes place.

Hormonal imbalance.—Moore & Ball (13) warn against an excessive reaction to trauma being converted into a hypoadrenal or extrarenal response by the occurrence of unsuspected adrenal failure or unrecognised and unreplaced extrarenal losses which place added burdens on the patient's economy. They note a second abnormality of the metabolic response in the "depletion response," by which is meant a reduced metabolic response to trauma in a person already depleted by illness, starvation, previous trauma, or operation. The present reviewer and his colleague Munro (23) had earlier found this to be so in the case of the rat. In addition to a less vigorous catabolic response in the depleted type of case there is a more "sensitive" convalescence: that is, the patient is more prone to develop complications such as venous thrombosis and wound dehiscence, and more readily develops hypoproteinaemia. Another abnormality of the metabolic response to trauma observed by Moore & Ball is considered to be a result of the hypoadrenal re-

There is no need to resort to tubal feeding unless the injury is such as to make this necessary, e g. facio-maxillary wounds. Parenteral administration apart from the critical shock period should not be necessary except where there is inability to ingest, digest, or absorb sufficient nutrients over a sufficiently long period as to place the patient's life in jeopardy.

Every device which can stimulate appetite should be used. This is generally easy if there is no concomitant infection. Where much tissue has been lost there would appear to be a proportionately higher demand for protein which we know to be best utilised in the presence of abundant carbohydrate: but a lost limb is not replaced as in a salamander. There may also be a special requirement for potassium and for riboflavin and ascorbic acid For those about to undergo operation it is strongly advised that within the time limit every effort should be made to improve the nutritive state of the body and, after the first few days following trauma, advantage should be taken of the heightened synthetic process in the reconstructive stage so that nothing is lacking for optimal convalescence.

The writer and others, notably Peters (35, 36), have considered that the negative nitrogen balance following injury, and certain other forms of illness, results from an excessive breakdown of existing protein rather than a failure of anabolism, including failure to utilise ingested protein even though this may also be a factor. The writer suggested that this breakdown was part of a reflex which took place as a result of injury and was bound up with the healing process so that a wounded animal, cut off from a supply of food, could survive for a time by catabolising its tissues to supply energy and the means of reparation (3, 5).

In their admonitions against the commonest abuses of this natural response to injury, Moore & Ball (13) warn against trying to treat the fever with antibiotics and against swamping the patient with water to make the urine volume up to an arbitrary normal during the early posttrauma phase. They are in agreement with the present reviewer in warning against trying to cover up the inevitable short-term nitrogen loss by giving unnecessary and poorly utilised proteins and protein hydrolysates intravenously immediately after operation. Whilst pointing out that the net loss of potassium is well tolerated, Moore & Ball are against allowing it to persist without replacement On the other hand, they advise against trying to treat the plasma sodium concentration. Like the reviewer, they also recommend not being overly concerned about a deficiency in energy intake for the first few days following the trauma: thereafter, they agree that every effort should be made to provide a diet of sufficient energy to obtain a positive nitrogen balance at the earliest possible moment Moore & Ball advise that 25 per cent of the calories in the diet be derived from protein This is a rather higher proportion than the present reviewer thinks necessary but sound evidence for the optimal level of protein is still lacking and it must be noted that some hold that it is sufficient to give a diet with a normal ratio of protein. The National Academy of Sciences and the National Research Council in their

exposure to cold. This supports the earlier work of Lathe & Peters on rats (29) who, in addition, could not reduce the excess nitrogen excretion resulting from cold or the excess nitrogen excretion from burning in the cold by methionine supplement.

Gribble & Peters (30) have found that the nitrogen loss following thermal burns in rats is largely abolished by thyroidectomy and that there is a suggestion that the decreased deamination of DL-alanine by liver slices of rats following burning is related to the modification of protein metabolism following the injury [Bekkum & Peters (31)].

In summarizing the effects of various hormones on the metabolic response attention is drawn to the adrenal cortex as essential for the full metabolic response of the organism to disease, though hypoactivity of the adrenal cortex may not be responsible in itself for the altered metabolism (9). It is obvious that in the present stage of our knowledge adjuvant endocrine therapy cannot be recommended, let alone be defined.

The tissue depletion which follows moderate to severe injury results essentially from two or more of five main causes: (*a*) loss of tissue, (*b*) loss of blood or exudate; (*c*) catabolic response to injury, and sometimes a loss because of (*d*) infection, (*e*) disuse, or reflex atrophy, or (*f*) a temporary loss into the zone of trauma.

Where there has been moderate or serious loss of blood or plasma, nutrition may be held to begin with early, rapid, and adequate transfusion. Browne *et al* (32) and Kremen (33) have shown that during the catabolic period plasma protein as such administered intravenously does not lead to an immediate rise in nitrogen excretion The former go so far as to say that a patient who is receiving plasma only may be regarded as being starved from this point of view even though he may be in apparent positive balance and though the plasma proteins may be exerting their colloidal osmotic pressure. The writer (4) found that despite substantial increase in the intake of a diet rich in protein and calories by patients with moderate or serious injuries a negative nitrogen balance generally existed at the height of the catabolic period The nitrogen loss was, however, mitigated by such procedures, a finding comparable to that described by Peters (34, 35).

While the patient's metabolism is in a catabolic phase, and the extent of the nitrogen loss is largely a measure of the nutritive state of the organism at the time in respect of protein, there appears to be no special need for concern about this loss in the previously well-nourished subject, provided steps are taken to replace rapidly and adequately the blood or plasma which has been lost by the nature of the accident or operation. As soon as possible the patient should be encouraged to eat to appetite a good diet. It is to be remembered that there may be kidney dysfunction during the first day or two and occasionally ulceration of the alimentary tract may result Peters (36) has strongly advised against trying to push nutriment into patients in the catabolic phase and has emphasized that there is no proof that incoming nitrogen can be utilized to prevent the losses consequent on injury at this time.

intestinal tract but it may be considerable from the lower portion of the tract. A prolonged potassium loss appears to delay recovery of normal visceral function and strength. This sets the stage for an acute drop in the plasma potassium concentration if trauma or alkalosis are superimposed. Since alkalosis in the surgical case is most commonly produced by chloride loss it has been recommended that the prevention of hypokalaemic alkalosis consist of the administration of potassium chloride. Wilkinson (37a) points out that the majority of patients after operation do not require intravenous infusion but when they show clear symptoms of potassium depletion intravenous therapy, including potassium salts, is of great value. It is necessary to use a replacement fluid which resembles in tonic composition that being lost from the body.

As was shown by Cuthbertson, McGirr & Robertson (14), potassium and nitrogen do not move in parallel. Moore & Ball have now shown that potassium enters and leaves the cell with greater speed than nitrogen, the result being a consistently high potassium-nitrogen ratio of both negative and positive balances. In the previously depleted patient the potassium-nitrogen ratio of the postoperative period is nearer to tissue composition.

When there are no extrarenal losses of body fluids it is recommended that sodium administration should be withheld postoperatively until after the fifth day. The use of large amounts of sodium early in the postoperative period is believed to overload the body with salt and therefore, with its associated water, ultimately produces hypoproteinaemia and oedema, and increases the extent of intracellular sodium shift. Extrarenal losses lead to, sodium saving, but these extrarenal losses should be replaced as they occur, for the volume of water in the normal extracellular space is depleted If not replaced, the volume of water in the extracellular space, or the sodium concentration in all extracellular water (including plasma), or both, must fall. There is no compensatory mechanism for the maintenance of base concentration in extracellular fluid.

Moore & Ball (13) postulate an intracellular sodium shift in sick surgical patients, particularly where severe trauma and renal sodium conservation complicate the situation, the sodium ion may move into body cells (probably muscle) as evidenced by the fall in plasma sodium concentration during the positive sodium balance phase after surgery. It may again rise during sodium diuresis. During the phase of sodium retention and falling plasma sodium concentration there is potassium loss from the body, and no weight gain. During the normal potassium gain phase there is sodium loss. The moral seems to be· treat the patient, not the sodium concentration.

Other specific dietary problems—After less severe forms of trauma or simple major surgery, fluids and solids should be advanced rapidly as tolerated to full diet, but after severe peritoneal injury, gastrointestinal anastomotic operation, etc , the progression has to be circumspect After extensive peritoneal damage or where ileus results it may take a week or more. In this case, progression is probably best by hourly feedings, but only if acceptable

Report (9) advise that all seriously sick and injured soldiers should receive 150 g. protein daily. Further investigation is required to determine this matter but the answer will not readily be found.

It must be noted that Levenson (37) believes that if malnutrition can be averted by early high food intakes it seems logical to do so. He instances the finding that children receiving from the start an intake one and one-half times that recommended by the National Research Council as optimal for normals remained in excellent nutritional status following severe burns Male adults (previously well) receiving an intake of 1.5 g. protein and 45 kcal./kg. body weight from the start show nutritional depletion if the burn is severe, but less than if this intake were not begun very early. Levenson considers that oral intakes begun at these levels on the first or second day of injury are well tolerated and that if there is a delay of a few days, then gastrointestinal upsets are much commoner. Continuous gastric drip feedings are stated to be better tolerated early than the usual oral feedings

It has been stated (9) that recommended dietary allowances for normal individuals are not applicable in calculations of therapeutic diets because of the demonstrable increased metabolic demands of disease and injury. The report points out that the extent to which the utilisation of, and requirements for, some vitamins are definitely modified, and may be increased during the acute phase of an illness or injury and also during convalescence, has not been defined. Further investigations into ascorbic acid and riboflavin metabolism in disease states are needed.

Food protein and intravenous protein hydrolysate are poorly utilised and retained in the early postoperative period, and this may account for apparent retentions observed by some investigators following trauma. In the type of case which shows the excessive response, it has been recommended that a larger fraction of the nitrogen intake should be given as intravenous whole protein and red cells, the nitrogen of which is relatively slowly metabolised. The writer doubts if satisfying evidence for this exists. Where extrarenal loss or other gastrointestinal disease may prevent oral feeding, parenteral hydrolysate feeding is apparently useful and these nitrogenous fragments are more rapidly metabolised.

Loss of blood by haemorrhage or of plasma protein by exudate and transudate can usually be prevented by quantitative replacements of these losses before water transfer from interstitial space has occurred. If hypoproteinaemia has become established from this cause the intravenous administration of protein concentrate is said to be the most effective treatment.

Electrolyte compensation.—Moore & Ball (13) advise that urinary losses of potassium should be made up quantitatively after the third day if there has been virtually no intake, provided there is no oliguria or anuria. Potassium losses may be compensated with ease by the oral route. If this is not possible an intravenous infusion of KCl at a concentration of 40 m eq. K/l. is recommended. One to 2 l. per day are said to suffice and may be given with glucose. Extrarenal loss of potassium is not great from the upper gastro-

The administration of protein hydrolysates intravenously is safe provided all the precautions are taken. It does not prevent the so-called catabolic destruction of protein tissue following a major surgical operation, and while not harmful, does not improve the condition of severely jaundiced patients. Further, as an antiacid protein hydrolysate plus sugar has been found inferior *in vivo* to whole or skimmed milk. As would be expected, the addition of fat to the hydrolysate-sugar mixture diminishes but does not abolish the inferiority. It has a stimulating effect on hydrochloric acid secretion (40).

The present writer has advised against the use of oral hydrolysates and against parenteral feeding except in situations where the patient's life is in danger if food cannot otherwise be supplied. It has been also pointed out that oral administered protein hydrolysates have little place in therapeutic nutrition (9). The newer developments in the use of intravenous fat emulsions are dealt with in the final section of this review.

UNDERNUTRITION

Quantitative Evaluation of Fatness-Leanness

The methods available for a quantitative evaluation of fatness-leanness applicable to living man have been reviewed by Brozek & Keys (41), who found that the most promising indirect method involves measurement of the thickness of the skin folds (subcutaneous tissue plus skin). There are three other techniques which should be noted but which are restricted in their usefulness for purposes of nutritional assessment: thickness of subcutaneous tissues plus skin from x-ray photographs, estimation of the total excess fat from the specific gravity of the body, and estimation of body fat from content of body water.

The low density of body fat makes possible the estimation of the fat content from the specific gravity. In man, the body volume needed in the calculation of specific gravity may be obtained as the difference between the body weight in air and when fully immersed in water The amount of air in the lungs must be taken into account (42) This method has been used in studying the effects of prolonged under-nutrition and of the rice-fruit diet (43).

It is also feasible to estimate the amount of total fat from the water content of the body on the basis that the lean (fat-free) body mass has a highly constant water content, as shown by Pace & Rathbun (44). Levitt & Gandino have recently reviewed methods for the determination of total body water (45) Using antipyrine, Messinger & Steele (46) obtained a satisfactory correspondence in nine individuals between body fat estimated from total body water and from specific gravity This finding has been confirmed by Osserman *et al.* (47) This technique cannot be applied easily in nutritional surveys Several years ago Welham & Behnke (48) pointed out that overweight for age and height by standard tables did not necessarily mean fatness, for in their group of professional footballers the men were 25 per cent above the army standards yet actually had a low fat content. Brozek & Keys (49) have

to the patient. Moore & Ball (13) recommend that these be of water or tea in the first instance, going on to more nutritious fluids, amounting to some 8750 kcal. The next stage in such cases as recommended by these workers takes the patient to little over 2000 kcal. level made up of the liquids as allowed in the earlier stages with enriched milk and other drinks and with soft solids being offered every two hours If required, the patient may remain on this diet for a week or two without any danger of developing deficiencies, providing he does not have large open wounds to close or a high fever. Progression beyond this usually leads to a full diet, but if not quite able to tackle this as in the postgastrectomy case and in those with diminished intestinal capacity, a six meal bland diet will probably be necessary. With such a diet in between meal feedings should not be large enough to destroy appetite. Moore & Ball in what they call a "fourth stage high protein diet" give three meals with extra nourishing drinks between meals on three separate occasions daily. Protein is now forming 17 per cent of the calories with the kcal. about 2700. Where maximum nourishment is required in minimum volume and in a form which is easily absorbed, high protein soft solids to 3500 or more kcal. can be given with protein forming some 15 per cent of the calories of the diet.

Tube feeding directly into the stomach may be necessary for special cases requiring to be fed in this way, e.g., gunshot wounds of the mouth. It has been recommended that the feeding should be intermittent at about 250 ml. per feeding. Some 1500 to 2000 kcal. can be given this way, similarly where jejunal feeding is required. The faecal nitrogen rises with jejunal feeding. A slow drip avoids mechanical distension of the jejunum which is the common est cause of cramp and diarrhoea with such feeding; if diarrhoea occurs, the volume should be reduced and small amounts of "half and half" milk and lime water substituted.

Co Tui *et al* (38) reported exceptionally good results in the treatment of peptic ulcer with large amounts of protein hydrolysate (Amigen). The improvement was stated to be so dramatic that in many instances surgical interference proved unnecessary. Their patients at the Bellevue Hospital, New York, were probably drawn from the lowest income groups and, because of their indigestion and their economic state, had been taking a very poor diet before coming for treatment. Treatment consisted of very large quantities of protein hydrolysate, 300 to 400 g./day along with 300 to 400 g. carbohydrate making up a ration of 2800 to 3200 kcal. of which half came from protein hydrolysate. The experience at Edinburgh Royal Infirmary of Billing *et al.* (39) was with diets of 2750 kcal. made up of 320 g. carbohydrate, 85 g fat, and 175 g protein (110 g. of which were as hydrolysate, the tolerance limit). Such supplements proved of no value in the treatment of patients suffering from peptic ulceration. In the preparation of poorly nourished cases for surgical operation these hydrolysates were found to be of limited value and in the immediate postoperate period they are, for various reasons, contraindicated

Although the value of 45 ml. of blood per kg. body weight has been used as a means of assessing the blood volume, lack of a close correlation has long been recognised. A similar lack of correlation between total body water and body weight has been noted, and recently Hardy *et al.* (52, 53) have observed a somewhat comparable condition in regard to plasma and also possibly in relation to extracellular fluid as measured by the thiocyanate method. It was found that plasma volume and also thiocyanate space were more closely correlated with total body water than with surface area, height, or body weight, observed or "ideal."

According to Edelman *et al.* (54) the plasma interstitial fluid pool acts as a single chamber for water distribution. However, according to Hardy *et al.* (53) the ratio of thiocyanate space represented a greater fraction of total body water in the obese than in very lean subjects. Greater penetration of fat cells by thiocyanate, displacement of intracellular water to the extracellular phase by fat, and increased available space between the fat cells themselves have been suggested as possible reasons for this observation.

Signs of Undernutrition

McCance & Barrett (55) have reported that undernourished people frequently have a peculiar pallor, and may of them a roughness and flaking of the skin, praticularly of the lower leg, which suggests an overproduction of keratinized cells. Sometimes the skin is fissured and folded, the raised areas being occasionally pigmented with plugs of hardened protein material often distending the hair follicles and sometimes with chronic ulcers on the lower leg The fat lies further from the surface than in normal people and the individual fat cells are small.

Studies on the circulation by these Cambridge workers have thrown little light on the aetiology of hunger oedema Although undernutrition had probably reduced the weight of the heart itself, the volume of the heart muscle and its contents was found to be within the normal range. Further, no significant difference in reflex vasodilatation was noted in undernourished and control groups after immersion of a finger in cold water, nor was evidence found that the capillaries in the upper limbs of persons suffering from hunger oedema were abnormally permeable when the venous pressure was increased, or that they were abnormally liable to injury by cold No evidence was found to support a claim put forward by Ickert (56) that undernourished people gave a specific response to running up and down a flight of stairs.

Concerning hepatic structure and function in chronic undernutrition Sherlock & Walshe (57) found that the hepatic histology was generally normal. The hepatic glycogen, fasting blood sugar, the oral glucose tolerance, and the epinephrin and insulin sensitivity tests were normal. (In passing, it is to be noted that in chronically ill, malnourished patients Brenner *et al.* (58) found an impaired eosinophil response to epinephrin) The hepatic alkaline phosphatase in the liver cells was normal in distribution and amount and that of the blood was also within normal limits. The concentration of total

also shown that men within plus or minus 5 per cent of their standard reference weight showed considerably larger depots of subcutaneous fat than younger men.

Location and Nature of Gains in Weight

It is important at times to know the location and nature of the gains in body weight following alterations in intake as well as the chemical compartments of the body which are being denuded during periods of loss in body weight. McCance & Widdowson (50) have made such an attempt. They used the thiocyanate method for extracellular fluid including blood, with a correction for penetration of thiocyanate into the erythrocytes and the total body water has been determined by measuring the volume of the body into which a known amount of urea distributes itself. The fat was determined by difference after making allowance for minerals. The difference between the total body water and extracellular fluid was termed "cell water" and on the basis of 67 per cent of water by weight of cell mass, the weight of cellular tissue was calculated. Previously, it had been determined that the minerals in the body were 6.2 per cent of the body weight or 7.5 per cent of the fat-free body with 0.5 per cent as compounds of potassium and phosphorus in the cells. This fat-free body is made up of the cell mass plus extracellular fluid and the minerals not included in the cell mass. From which it was calculated that the minerals in the bones and extracellular fluids account for $(7 \times 100)/93) = 7.5$ per cent of the combined weight of the cell mass and extracellular fluid. When applied to ten normal and obese male subjects whose gross individual weight varied from 72 to 190 per cent of the standard weight for height data (51), the extracellular water varied from 25.5 per cent of the total weight in a lean person to 14.8 per cent in an obese subject. The cell mass in the leanest person was 60.8 per cent, whereas in one of the obese subjects this value was 37.3 per cent. The fat in these two subjects was 7.2 per cent in the lean and 44 per cent in the obese. In 11 women the extracellular water (24.8 to 14 7 per cent) again was greatest in the lean individuals as was the cell mass. In the normal women there was more fat than in the normal men and one obese subject had 58.1 per cent of the body weight as fat.

An examination was made by these Cambridge workers (50) of 10 undernourished Germans when they had been released from a prison camp in Russia and again two months after rehabilitation had been in progress in a hospital, with generous food allowances but in most cases with little exercise. Before realimentation these male prisoners had much more extracellular water (30.2 to 46.2 per cent) in their bodies than have normal subjects, a characteristic feature of undernutrition. The cell mass in these men before refeeding made up a strikingly low proportion of the body weight (36.2 to 55.5 per cent) and the percentages of fat were small, most of them being at the low border of the normal range. With rehabilitation, the extracellular fluid decreased and the cell mass and the body fat increased. The ratio of the fat phase to the aqueous phase was still abnormal after two months.

development of clinical oedema there was practically no decrease in the total protein concentration. Normal serum protein levels have also been found in "famine" oedema (63). In discussing the history, significance, and aetiology of hunger oedema, McCance (67) suggests first that the paucity of information about what is a characteristic feature of undernutrition is because the metabolic effects of a shortage of food were masked by great epidemic diseases that always accompanied famine and undernutrition till well into the present century; secondly, that between the two world wars its importance became very much overemphasised.

The essential abnormality of the body water in undernutrition is the increase in the percentage of the body occupied by extracellular fluid: visible oedema is only one aspect of this, and many people never exhibit it. There are probably several causes both for the increase in extracellular fluid and for the appearance of pitting oedema. It is suggested that the replacement of body space previously occupied by fat and cellular tissue is an important cause of the increase in extracellular fluid. If and when there is a fall in the concentration of serum proteins it is natural to suppose that this will also operate, and a large intake of salt must also help. The appearance and disappearance of visible oedema in man is undoubtedly connected with posture, and the presence in the body of so much extracellular fluid free to move under the influence of gravity. It is natural to suppose that a reduction in muscle size and intercellular colloid, and a loss of elastic fibres from a skin now too large for the structures it was designed to enclose, will all favour localized collections of fluid in the dependent parts

Although Localio and his associates (68) demonstrated by their biopsy method that depletion of fascial and muscle protein occurred at a time when the serum protein concentration was within normal limits, this method is not likely to be a very sensitive or even a practicable method for routine use.

Reduction in blood volume complicates the interpretation of the concentration of plasma proteins. Without a measurement of total blood and plasma volumes, the concentration of the plasma protein may be misleading, but even here caution is needed unless fractionation of the proteins is carried out. Weech (69) noted that, in contrast to the fall in the albumin fraction which commonly occurs in the protein-depleted individual, the serum globulin remained *relatively unchanged. Zeldis et al (70) and Chow (71, 72)* confirmed the marked decrease in albumin in dogs but noted that while the γ-globulin tended to be slightly lowered, the circulating α-globulin remained normal or even increased These last workers used electrophoretic methods These methods are generally found to be of the greatest value Salting out and precipitation methods give useful though limited information

The response of the total circulating proteins to a saline infusion is reckoned by Pollack & Halpern (63) to be the simplest objective index available for evaluating the status of protein nutrition The basis of this test, which dates back to Shearburn's observation (73) on dogs, is that the labile stores enter the blood stream quite rapidly in an attempt to maintain os-

cholesterol in the serum was often low and that in ester form also. The intravenous hippuric acid synthesis test gave normal results.

McCance, Dean & Barrett (59) confirmed the finding of enlarged parotid glands in men who were rapidly gaining weight after being repatriated from camps for prisoners of war. These men did not have enlarged breasts as Spinzels (60) has described.

The Evaluation of Protein Nutrition

When a specific amount of a tagged amino acid such as glycine was administered in the diet to the well nourished organism (61) approximately 70 per cent was retained When the same amount was given when the diet was high in protein only about 40 per cent was retained. When tagged ammonia was added to a diet of average protein content it was nearly quantitatively excreted but when the diet was very low in protein an appreciable fraction of this ammonia nitrogen might be used in protein synthesis (62). It has been shown that the utilisation of ammonia nitrogen by human subjects in prolonged starvation can be nearly as high as the utilisation of glycine nitrogen by subjects in a good state of nutrition.

Pollack & Halpern (63) reviewing the literature conclude that all organs and tissues, including blood, will exhibit variations in their protein content at different levels of protein intake. In the course of protein deficiency the source of the so-called "reserve" protein shifts from the labile organs to those organs which change slowly. A limited percentage of this protein may be lost during protein starvation without apparent serious physiological disturbance It may also be reaccumulated.

The behaviour of the patient on a nitrogen balance may indicate the previous nutritive state in respect of energy and protein If a negative nitrogen balance in the face of adequate calories and protein is found, as in the case of an acute febrile illness, fracture, or other moderate to severe trauma, the negative balance which is generally established is an indication of satisfactory nutritive state as concerns protein. Failure to develop this negative balance has been shown to occur in laboratory animals and in men who are in a depleted state in regard to protein (23, 64). It is important to appreciate that wasted and chronically ill patients may readily show positive balances despite serious injury or disease.

Various other tests for determining the protein status of a patient have been devised. Pollack & Halpern (63), reviewing the methods used, find that determinations of the plasma proteins do not give a very satisfactory index because they do not reflect accurately the proteins in the tissues as the body tends to maintain the serum protein at a nearly normal level, this homeostasis being achieved by supplies from tissue proteins in somewhat the same fashion as the serum calcium is maintained irrespective of the state of the body reserves (65).

Keys and his colleagues, in their study of human starvation (66), found that despite a loss of an average of 24.5 per cent of the body weight and the

blood cells. No changes were found in the red cell enzymes comparable in magnitude or interest with the fall in the activities of P- and T-cholinesterases which occurs in the serum in undernutriton. No alteration in the sedimentation rate was found in uncomplicated undernutrition, nor was there any suggestion that large quantities of diastase were excreted.

Although the aetiology has not been fully established, many regard the condition of kwashiorkor to be a result of protein deficiency. Thompson & Trowell (88) consider that certain features of the condition of kwashiorkor indicate a failure of digestion, absorption or both, as the diarrhoea is frequently associated with bulky unformed stools in which particles of undigested food are often seen. This suggestion of a digestive failure is supported by the fact that many children take an adequate caloric intake for normal growth and yet fail to gain weight. Whereas clinical observation suggested a digestive or absorptive upset, histological evidence indicated that the disorder might be pancreatic in origin. In their investigation of this Thompson & Trowell found that there was a significant depression of lipase, amylase, and trypsin concentrations in the duodenal contents of children with established kwashiorkor and there was evidence that this defect was reversed in all children who received a high intake of milk protein and in whom intercurrent infections, if present, were treated.

Wills (89) points out that three very constant ill-effects generally result in populations which subsist predominantly on carbohydrates: (*a*) the development of a macrocytic anaemia when under stress; (*b*) the development of fatty livers in children and a high incidence of cirrhosis and malignant disease in the adult; (*c*) muscular wasting and an abnormally low level of serum albumin; with the last is associated a tendency to develop oedema. These effects are primarily a result of inadequate protein and in addition there are often indications of deficiencies due to the absence of associated members of the B complex. Wills also considers that the evidence in favour of a deficiency of animal protein in kwashiorkor is suggestive but it has yet to be demonstrated that adequate calories from mixed vegetable staples can prevent the syndrome and give maximum health. Milk is certainly the basis of successful treatment. The observations of Rhodes (90) point to deficiency of animal protein or possibly an "animal protein factor" as a factor in the production of liver disease amongst Jamaican children whose sole source of animal protein was sweetened condensed milk, probably a comparable condition to kwashiorkor.

Proteins for artificial milk.—In a search for a substitute for the protein of milk in compounding an artificial milk for human infants which can be used at the transitional stage between breast milk and the adult diet, Dean (91) considers that we have now sufficient evidence to show that it is possible to evolve diets containing protein exclusively from plant sources which will successfully rival diets containing fair amounts of animal protein There are still many difficulties to be surmounted; for example variation in the amounts of amino acids in the raw materials, depending on the strain of

motic equilibrium. Harroun, Smyth & Levey (74) have recently demonstrated that this change in content of circulating protein following a test infusion can be used in man to demonstrate the existence or absence of adequate stores of protein. In well-nourished individuals the direction of flow was into the blood stream and the total circulating protein increased by an average of 13.6 g., whereas, in the undernourished, protein left the circulation. The average decrease of the total circulating protein was 14.7 g. In these cases it was only the change in the total circulating proteins and not their absolute amount which correlated well with the apparent status of the protein reservoirs.

An attempt by Levey *et al.* (75) to determine if the excretion of nine individual amino acids following their intravenous infusion, would serve as a guide to protein status proved ineffective, as the retention of the individual amino acids could not be correlated with the subject's nutritional state.

For the optimal use of protein the diet must be adequate in calories, vitamins, and minerals, and the carbohydrate must be fed at the same time as the protein or within a short time after (76, 77, 78). Protein utilisation is best effected when it is eaten along with carbohydrate or at least within a short time of the eating of carbohydrate.

Gell (79) found that the response of a group of undernourished persons to an antigenic stimulus was significantly less than that of a normal control group. No correlation was found between immune response and weight loss or with the level of serum proteins. Kekwick (80) examined the electrophoretic pattern of the sera of cases of undernutrition but found no consistent deviation from normal except a slight reduction in the proportion of albumin There was no correlation between the concentration of albumin in the sera and the occurrence of oedema in the patients.

The arginine to lysine ratios of the serum protein were found to be within normal limits (81), thus not substantiating workers such as Florkin & Duchateau (82) who have thought that it was lowered by undernutrition.

Enzymic activity—Following up clues from the work of Milhorat (83), who noted that cholinesterase activity of the serum in a case of anorexia nervosa varied with well being and body weight, and the observations of Faber (84) and Kaswin (85) which indicated that the cholinesterase activity of the serum might be affected by the state of nutrition, Hutchinson [illegible]

the mean activities of groups of people at different nutritional levels, and (*b*) by studying the effect of additional food The rise was due to the gradual gain in weight and well-being brought about by the better diet rather than to any major dietary constituent.

Certain negative findings were found by Hutchinson (87), namely that undernutrition, even if fairly severe, probably does not raise or lower the activities of T-cholinesterase, phosphatase, catalase, or glyoxalase in the red

if he had remained on this diet the whole time. It is perhaps wise to regard these statements as an inducement for additional investigation, particularly in the light of the work of Walker, Fox & Irving (93a).

The amount of phytate hydrolysed in the intestine to inorganic phosphate depends partly on the amount of calcium in the diet, and varies with it (94). According to Mellanby (95) it would not matter if it were hydrolysed or not if the body contained no vitamin D, for in puppies it is only in the presence of this vitamin that phytate has a greater anticalcifying action than phosphate. "Adaptation" through an increasing ability to hydrolyse phytic acid in the intestines while the intake of calcium and phytic acid remains the same, if it does occur, is thought to occur high up in the intestine for the calcium to be absorbed and is presumably brought about by some change in the reaction of the intestine.

Effect on Reproduction

In view of the definite evidence that in some species the state of nutrition of the mother, particularly during the last part of the pregnancy when the foetus is growing very rapidly, has a definite effect on the size of the foetus, an analysis was made by Dean (96) of the births at the Landesfrauenklinik, Wuppertal in Germany, during the years 1937 to 1948. In 1945, the year when there was probably the greatest shortage of food, the average birth weight was 185 g. less than in 1937, a fall less than has been attributed to undernutrition in other countries and represented a loss of about 6 per cent of the average weight in 1937. A very small reduction in length accompanied the reduction in weight. The period of gestation was slightly shortened, but not enough to account for the reduction in weight. The children took considerably less breast milk in 1945 to 1946 than in 1937 to 1938. Dean concludes that the state of nutrition of the mother must have played some part in the production of the changes. Anxiety of the mother may have contributed to the failure of lactation No significant change in the quality of the breast milk could be detected [Gunther & Stanier (97)].

Realimentation Phenomena

Although the studies on prisoners liberated from concentration camps had provided much of interest, there was frequently concomitant disease. After McCance's unit had been working at Wuppertal for several months and the characteristics of the undernourished individual had been fairly well defined, a study was made on the effects of giving such a group an adequate diet. Although Keys, *et al.* (98) had made most careful studies of a diet providing 2020 to 4228 kcal a day on men who had voluntarily submitted themselves to undernutrition, Widdowson (99) considered that these men would have eaten much more food and recovered more rapidly had they been given the opportunity of doing so. On the average intake of 6,000 kcal a day 19 undernourished men whose ages ranged from 26 to 80 years increased by 10 kg during the eight weeks and the older men gained almost as much

wheat or yeast, for instance, or on the method of cultivation of rice; alterations in biological value caused by heating and by the reactions between amino acids and sugars, reactions whose significance may escape detection by the ordinary methods of analysis; variations in the methods of preparation of foods which may impair digestibility and cause loose stools; economic problems, etc.

One of Dean's most successful mixtures was 25 per cent of the protein from barley, 5 per cent from wheat and 70 per cent from soya. The removal of the trypsin inhibitor in the soya increased its nutritive value. It was necessary to give a higher proportion of protein in the cereal-soya diets than in the milk diets

As the soya bean cannot be grown well in the United Kingdom, Dean (91) is conducting an investigation on sunflower seed protein which is said to contain twice as much of both lysine and tryptophan as maize protein. It has been found that rats grow excellently upon various combinations of sunflower and maize, especially if a little yeast is added to the diets.

Absorptive Conditions

Berridge & Prior (92) report having discovered no cases of osteoporosis or osteomalacia in Wuppertal at the end of the War.

In an investigation of the absorption and excretion of nitrogen, calcium, magnesium, and phosphorus and on the basis of antecedent literature Widdowson & Thrussell (93) consider that raising the intake of phosphorus, and particularly of phytic acid phosphorus, depresses the absorption of calcium. If the calcium and the phytic acid phosphorus intakes are increased together, so that the proportion of the one to the other remains the same, then more calcium will be absorbed, possibly because the absolute amount of calcium in solution in the intestine will have been increased

The observations of these workers permit them to state that: (*a*) an adult who has been accustomed to a high calcium diet, and who has been absorbing enough calcium to maintain himself in calcium equilibrium on this diet, would absorb less calcium if his calcium intake were reduced or his phytic acid intake increased, and if the diet were sufficiently poor in calcium or rich in phytic acid he would probably be in negative calcium balance; (*b*) if he continued to eat this diet he might, after some time, come into calcium equilibrium again, but his bones would have lost some of their calcium in the process; (*c*) a child who has been absorbing sufficient calcium to maintain himself in positive balance on a high calcium diet would likewise not absorb so much calcium if his calcium intake were reduced or his phytic acid increased. If this diet had produced a negative calcium balance he might, after some time, start to retain calcium again, but his bones would not contain less calcium than if he had continued to eat his original high calcium, low phytic acid diet; (*d*) if such a child or adult who has become "adapted" to a low calcium high phytic acid diet, then returned to his original high calcium low phytic acid diet he would absorb and retain far more calcium than

blood cholesterol, and that the cholesterol is synthesised from this fat. Adding more cholesterol to the diet did not raise the level. Keys recommends a restriction of total caloric intake and restriction of total extractable fats to 25 per cent to 30 per cent of total diets. Geiger (103) recommends a low fat, low cholesterol diet so long as it does not interfere with the well-being of the patient. His emphasis on the dyscrasia of the blood as the primary injury is open to debate

The present reviewer believes that a study of the tissue metabolism of the normal and atheromatous arterial wall is overdue and that a combined approach involving biochemical, electron microscopy, x-ray diffraction pattern, and histological methods should be carried out on adjacent tissue slices and might prove a guide.

NEWER KNOWLEDGE OF VITAMINS

Space permits only two main references. The first of these concerns niacin; the second, vitamin E.

In Mexico there is very little primary pellagra although there is a high consumption of corn ("maize" in the British literature) and a low intake of animal protein by some sections of the community; conditions which in other parts generally lead to pallagra. One difference, among others, between the Mexican conditions and those pertaining to pellagra areas is that the corn in Mexico is eaten in the form of "tortillas" prepared in the first stage by cooking the whole corn in lime water. Laguna & Carpenter (104) have found that the growth depression of rats fed a high corn diet, in the absence of niacin, was reduced by steeping the corn in lime water, then neutralizing and drying it, a process similar to the one commonly used by generations of Mexican peasants in making their "tortillas" Corn reconstituted from the fractions obtained on wet milling did not show this enhanced effect, being no different in its effects from the untreated material. The full effect of the lime-water treatment was obtained by treatment of the nonstarchy fractions—gluten, germ, and feed meal.

These experiments serve as a starting point for further investigations, but these must also be carried through with corn cooked in those areas having a high incidence of pellagra. Meantime, the present experiments re-emphasize the importance to health of many of the cultural food patterns of man, for here we have an age-old custom which provides a source of calcium to peoples not consuming milk or milk products, and also apparently provides or liberates a source of the vitamin, niacin.

In Copenhagen, Dam *et al.* (105) made a remarkable discovery in finding that methylene blue, thionin, and thiodiphenylamine caused a marked improvement of the growth of vitamin E-deficient chicks which was comparable to that resulting from the administration of α-tocopherol acetate. The action of methylene blue against the exudative diathesis and encephalomalacia was so clear-cut that Dam and his colleagues (106) were prompted to test the effect of these substances on vitamin E-free diet on liver storage of vitamin A.

as the *younger ones.* There was a significant rise in pulse rate, basal oxygen consumption, serum and blood volume, haemoglobin and haematocrit levels, serum protein concentration, and cholinesterase activity as a result of the *unrestricted diet.* There was little or no change in arterial pressure and body temperature or in the incidence or degree of oedema. The extracellular fluid volume was high at first, and there was a reduction in the absolute volume as well as in the volume expressed *as a percentage of the body* weight. There seemed to be little or no correlation between the volume of extracellular fluids and the amount of clinical oedema. The men were examined periodically for two years after their *return to the German rations.* At the end of this time their weights were lower than they had been at the end of the experimental period, but their haemoglobin, haematocrit, and serum protein levels were higher. Their oedema had *almost disappeared.*

OVERWEIGHT

It has long been known that it is more dangerous to be overweight than underweight, and the recent study in the United States by Armstrong *et al.* (100) has again drawn attention to the fact that compared with the number of patients who develop deficiency diseases those who are even 20 per cent *over what has been considered to be the ideal weight is astronomic,* being in the region of 5 million or more In their study of 25,998 overweight men and 24,901 overweight women (10 per cent or *more above the ideal weight)* it was found that the mortality in the case of the men was one and a half times that of insured men of ideal weight. Men with marked obesity had almost double this mortality figure. The overweight women had an overall mortality which was of the same order, though the recorded mortality in the markedly obese was rather less. It is not only sound sense to give a restrictive sub-calorie diet to the obese but, according to Dunlop (101), it should not be forgotten *that many cases of flat feet, varicose veins, ventral hernia,* oesteo-arthritis of the knees and hips, gall stones, diabetes, heart disease, hypertension, and bronchitis go with obesity.

Human atherosclerosis and the diet —It seems pertinent in this context to refer to the recent report of Keys (102) ,which points to excessive calorie intake with resulting obesity as the one definitely related factor in this condition He considers that conclusions relating the development of atherosclerosis in animals fed high cholesterol diets to the development *of* atherosclerosis in humans on high cholesterol diets are not valid because of the great disparity between the very high amounts of cholesterol fed to experimental animals and the amounts that human beings take even on a "high cholesterol" diet. That there is a relationship between high levels of serum choles-

from animal or vegetable sources, is the significant factor in the level of

periment on Ayrshire calves which were given a basal diet containing dried skim milk, lard, and a mineral supplement, it was found that when the necessary vitamins A and D were given as the pure substances in arachis oil with and without 50 mg. DL-α-tocopherol acetate daily, muscular dystrophy occurred in the unprotected group. When cod liver oil was substituted for the pure vitamin in arachis oil muscular dystrophy also occurred irrespective of the addition of the α-tocopherol. Post mortem examination of the affected calves revealed an extensive bilateral and symmetrical dystrophy with oedema, involving both skeletal and cardiac muscles. The daily ingestion of 15 to 18 ml. cod liver oil neutralised the protective action of 50 mg DL-α-tocopherol acetate daily. The disease appears quite comparable to the white muscle disease of Vawter & Records (115) and the waxy degeneration noted by earlier authors in farm animals.

The results in the muscle can be described by assuming a major change in the synthesis, or destruction, or both, of globulins in dystrophic musculature An increase in fat, cholesterol, lipid phosphorus, stroma protein, and collagen as well as oedema of the muscle could be accounted for in this way. Secondary changes accounted for the calcification and part of the increase in nucleic acid content.

The unsaturated fatty acids of marine liver oils, notably cod liver oil, linseed oil, possibly also arachis oil and lard, are of importance in increasing body demands for vitamin E. Rapid deterioration of diets with consequent destruction of vitamin E has also to be considered and there is ample evidence that when such deterioration occurs, Vitamin A activity is also destroyed (115a).

Intravenous Feeding with Fat Emulsions

In situations where it is necessary to resort to intravenous alimentation, one of the major problems has been to provide sufficient energy in a tolerable volume of fluid Whilst the parenteral feeding of emulsions of fat has been tried at intervals for half a century only recently has success been achieved There still remain the problems of the occasional pyrogenic reaction and, more rarely, nausea followed by transient vomiting On the basis of their recent successful experience with 10 to 15 per cent fat emulsions of particle size less than 1 μ in diameter, prepared by a homogenization process and utilising a phosphatide stabilizer and a co-stabilizer in low concentration, Van Itallie *et al.* (116) gave a stable fat emulsion for a period of 36 days to a case of complete intestinal obstruction resulting from generalized peritonitis. One injection of the fat emulsion was given intravenously each day and averaged 1173 kcal. per day, the kcal. from sources other than fat being 1100 per day. For 31 days prior to the introduction of the fat the patient had been on alcohol, glucose, and protein hydrolysates in liberal amounts, but had nevertheless become increasingly cachexic. After 67 days of complete parenteral nutrition, the patient began to retain small amounts of food orally and parenteral feeding was discontinued His intake by mouth soon

With the diet containing 10 per cent cod liver oil the administration of methylene blue, thiodiphenylamine, and tetraethylthiuram disulfide (Antabuse) all caused an increased deposition of A in the liver and significantly increased the growth rate and the effect was comparable to that resulting from α-tocopherol or its acetate. Since neither methylene blue nor tocopherol acetate had an effect when the cod liver oil of the diet was replaced by lard it was concluded that the protective action of vitamin E and of its substitutes had consisted not of a direct action on vitamin A, but one of detoxication of some of the components of the cod liver oil which would otherwise decrease both vitamin A stores and growth rate, possibly through liver damage. Vitamin E and related substances do not seem to exert their protective action on vitamin A stores by effects on digestive processes.

Dam & Granados (107) have shown that the massive hepatic necrosis of Himsworth and his colleague Glynn (108, 109) and György & Schwarz (110) does not appear if the diet is free from fat. On the other hand it appeared when lard or even more so when cod liver oil was incorporated in the diet. Addition of methylene blue at a 0.126 per cent level gave complete protection and was superior to the addition of tocopherol.

The possible replacement of vitamin E by methylene blue as an antisterility factor was studied in females by Dam & Granados (111), who found that methylene blue improved markedly, and to about the same extent as tocopherol acetate, the much impaired reproductive capacity of female rats reared on a vitamin E-deficient diet, "fat-free," and cod liver oil containing diets.

Dam and his colleagues have just reported that a muscular degeneration grossly manifesting itself as white striation (for instance of the breast muscles) can be produced in chicks with vitamin E-deficient diets containing no added fat (111a). It would appear wise at this juncture not to deduce from these experiments that vitamin E can replace methylene blue in all its characteristic biochemical reactions

The fact that methylene blue seems to be inactive against certain vitamin E deficient symptoms, such as muscular degeneration in chicks on a fat-free diet, does not exclude the possibility that in such cases, vitamin E acts as an antioxidant The antioxidant effect may not necessarily be related to fats or have to take place in the tissue where the deficiency symptom appears. According to Dam (111b) the bulk of the information shows that vitamin E exerts an important function as an antioxidant in the body, thereby acting as a moderator fending off the otherwise noxious consequences of a series of dietary imbalances and preserving certain metabolites. As long as no other explanation is on hand it might be assumed that the reduced reproduction capacity in animals is also because of the lack of protection of certain essential metabolites, e.g., essential fatty acids, amino acids, or other compounds.

Another interesting observation on vitamin E falls to be recorded for a dietary deficiency of α-tocopherol resulting in muscular dystrophy has recently been described by Blaxter and his colleagues (112, 113, 114). In an ex-

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reached adequate levels. Ten days later the patient was convalescing satisfactorily.

This group of workers has given as much as 2 l. of fat emulsion, providing 3200 kcal., in a 12-hr. period without untoward response. No evidence of damage to liver or disturbance to the integrity of the red cell membrane has so far been found.

The experiments of Lerner *et al.* (117) on the oxidation of parenterally administered C^{14}-labelled tripalmitin emulsions justify the conclusion that emulsified fat introduced directly into the blood stream is available for caloric purposes. Further evidence that parenterally administered emulsified fat pursues a normal metabolic path was provided by the finding that about 50 per cent of the injected C^{14}-labelled fatty acids recovered in the liver had been incorporated into phospholipids at the end of 24 hr.

The observations of Meng (118) have shown that in dogs injected fat is transported from the blood stream to the lymphatic system partly by direct transfer through blood capillaries of the liver, intestine, and adipose tissues, where the fat is transformed and desaturated, joining the thoracic duct via their respective lymphatics.

Van Itallie *et al.* (116) conclude that the question of feasibility of administration of fat is now beside the point and that future work should be concentrated upon the production of a consistently stable and nonpyrogenic product.

Coeliac Disease

The first real break in our knowledge of the fundamental abnormality in this disease has arisen from the observations of Dicke (119) in Holland, who showed that patients with coeliac disease improved when wheat and rye flour were excluded from their diet. Weijers & van de Kamer (120) demonstrated that there was a decrease in faecal fat under these circumstances and that the reintroduction of wheat flour, though not of wheat starch, into the diet led to deterioration. Anderson *et al* (121) have confirmed this and have shown that it is the gluten fraction which has the harmful effect. Now as reported at the First International Congress on Dietetics at Amsterdam, Weijers, van de Kamer & Dicke have found that rye as well as wheat exercises this harmful effect. The decisive factor seems to be gliadin They also consider that fat absorption is not disturbed in coeliac disease but that a fat excretion exists. According to an unpublished report by Weyers & van de Kamer (122) the disastrous effect of wheat flour can be checked by niacin.

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ALLERGY[1,2]

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Progress in the field of allergy during the two-year period covered by the current review has been considerable. Continued experience with the newer therapeutic agents, antihistaminics, ACTH,[2] and cortisone, has led to fairly stable conclusions regarding their clinical usefulness and, perhaps more importantly, to wide-spread interest in their exact modes of action. The basic questions of antigen metabolism and antibody production and their differences in the allergic and non-allergic subject remain unanswered and the question of the mechanism of the malign effects of antigen-antibody unions in general is by no means solved. However, techniques for an approach to these problems are at hand and progress is being made.

Antigen metabolism.—The possibility of using radioactive tracers as labeling agents in following antigen metabolism has received preliminary attention. Bukantz *et al.* (1) have investigated the time sequences involved in the metabolism of antigens by following in normal rabbits the disappearance rates of tracer labeled bovine albumin, normal γ-globulin, and γ-globulin that had been altered chemically by azo conjugation or iodination to saturation. The rates of disappearance observed were compared with those found in animals after total body irradiation, active immunization, passive immunization, and after a specific anamnestic response had been awakened. Radio-labeled γ-globulin disappeared from the circulation in three phases: 75 per cent in 24 hr., 92 per cent in 96 hr., and virtually 100 per cent in nine days. It was never retained in or concentrated by tissues. Complement fixing antibody appeared by the seventh day, was maximal at the tenth, and disappeared by the twentieth day. In contrast R-salt-azo-biphenyl-azo γ-globulin and *p*-amino benzoic acid-azo γ globulin disappeared from the circulation precipitously, 90 per cent loss in 6 hr. and 99 per cent loss in 24 hr., and were retained in the RE macrophages of several organs, notably spleen, liver, and lymph nodes, with an approximate tissue half-life of 3 to 7 days. The iodine saturated antigen left the circulation as rapidly as azo antigens, with less tissue retention. Urine excretion of I^{131} containing protein breakdown products reflected the blood and tissue elimination of antigen. X-ray (300 r or more) did not affect the nonimmune rate of elimination of antigen, although the immune response was suppressed. The intravenous injection of antibody to radio-labeled γ-globulin produced a prompt decrease in circulating antigen in proportion to the amount of antibody injected. Finally, in a specific anamnestic response, antigen

[1] The survey of literature pertaining to this review was completed in September, 1952.

[2] The following abbreviation is used in this chapter: ACTH (corticotropin).

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of antigens responsible for the development of natural antibodies to red cells (for example the blood group antibodies and cold hemagglutinins) call attention to the presence in bacterial and animal parasites of antigens related to the blood types. Polysaccharides of similar chemical structure have been isolated both from capsules of pneumococci and from secretions possessing blood group specificity. A chemical explanation for the presumed heterogenetic development of blood groups is thereby afforded. Crawford *et al.* (14), in a further discussion of the heterogenetic origin of anti-A antibodies, provides evidence that the heterogenetic stimuli studied in their patients, namely injections of typhoid vaccine and antitetanus serum, produced an anti-A body differing from the naturally occurring anti-A bodies in heat stability and in incompleteness as shown by failure in itself to induce hemagglutination. This variation in antibody response from the accepted normal and its interrelated problem of antigen metabolism recalls the earlier work of Treffers, Heidelberger & Freund (15) upon the importance, among other things, of the factor of route of injection in determining the type of antibody produced Their work showed that the intravenous injection of horses with alum-precipitated rabbit serum globulin resulted in the production of antibody which gave a typical precipitin reaction without a prezone in the region of antibody excess The chemical, physical, and serological properties of the antibody were comparable to those of the more familiar anticarbohydrate antibodies The subcutaneous injection of horses with the globulin antigen on the other hand gave rise to low grade "univalent" antibody which did not precipitate with soluble antigen. The low grade antibody could be removed from solution by attachment to preformed specific precipitates, or by co-precipitation in the presence of "multivalent" precipitating antibody. It was concluded that the familiar antitoxin type of antibody is is not the only form of antiprotein response in horses but that both precipitating and low-grade nonprecipitating antibodies may also be formed The route of injection as well as the nature of the antigen was shown to be an important factor in determining the characteristics of the antibody obtained.

The possibility of antigen reacting with or being modified by the tissue into which it is primarily placed is of considerable potential importance in explaining variations in antibody response. The observations of Eisen *et al.* (16) on the elicitation of delayed allergic skin reactions with haptens are perhaps cases in point Of a group of eight 2,4-dinitrophenyl compounds with a high degree of configurational uniformity, only those compounds that combined with skin protein were capable of eliciting a delayed allergic reaction Similarly, on the quantitative side, Walsh & Smith (17) have demonstrated that a polymorphonuclear exudation at the site of antigen injection is followed by an antibody titer that is lower in the case of the pneumococcus polysaccharide antigen than is that associated with a macrophage response at the site of injection. Evidently the problem of antigen metabolism in normal and abnormal tissues and hosts is at best complicated. It is fraught with further difficulties when the system studied requires that

disappearance during the first two days was at the usual nonimmune rates and a typical immune rate began at the third day.

Latta (2) in earlier studies has also provided estimates of the organ and extracellular fluid distribution of I^{131}-labeled foreign protein antigens in rabbits and their rates of disappearance. In somewhat similar experiments, Crampton & Haurowitz (3) were able to show that the bulk of their radiolabeled antigen might be recovered in the mitochondrial fraction of tissue homogenates. Later studies (4, 5) have indicated that their pattern of intracellular distribution is a function of time and the size of injection. The observed presence of antigen in the mitochondrial fraction is exciting (6), but the possibility of artefactual association of antigen with mitochondria in the course of cell disintegration needs assay. An intracellular location of at least a portion of the injected antigen seems plausible however, and Coons' (7) work with fluorescent labeled compounds demonstrates an intracellular accumulation of pneumococcus polysaccharide in the nuclear sap, a location fitting rather well with the template model of antigen-antibody production and deductions concerning nuclear and cytoplasmic relationships in the synthesis of protein (8, 9). Further exploration of this field will be awaited with interest.

From a survey of evidence relating to the problem of the origin of natural antibodies, the nature of the antigen involved, and the type of host response awakened, Weiner (10) has concluded that with some rare exceptions natural antibodies, such as hemagglutinins and hemolysins, are of ordinary immune origin. These antibodies, like those generally conceded to be of immune origin such as Rh antibodies, occur in the univalent as well as in the multivalent form. Their persistence throughout life is not much different from that observed in experiences with Rh sensitization in which antibodies induced by deliberate immunization have been shown to persist indefinitely, after all apparent contact with the antigen has ceased. This seemingly low order of requirement for template renewal is similar to that observed in the experiments of Heidelberger *et al.* (11) in which amazing persistence of antibody is observed in human subjects following injection with pneumococcal polysaccharides. One would like to know more about template renewal versus antigen persistence in these several instances.

The general opinion (10) is that natural immunity to bacteria and viruses is also of immune origin. It is the result of undiagnosed or symptomless infection. This point of view has received support from the observations of Gillespie and co-workers (12) on the serological relationships existing between bacterial parasites of the intestinal tract and their hosts. His observations in addition raise the question of why certain normal intestinal coliforms stimulate antibody formation and others do not and why the stimulation is observed in some individuals and not in others—a rather basic question similar to that of why some people develop pollen allergy and others with equal pollen exposure do not.

Both Weiner (10) and Francis (13), in discussing the heterogenetic origin

venous injections of paratyphoid B vaccine. One to four days after the last immunizing injection both white and red splenic pulp and splenic cell suspensions were found to produce agglutinins when explanted in vitro At the height of antibody production, three to four days after injection, red pulp material was found to produce more agglutinin than white pulp. In agreement with Fagraeus (31, 32), the characteristic aggregates of immature lymphoid cells, considered to be immature plasma cells, were always found in the red pulp at this time. In preparations of splenic cell suspensions, both large immature lymphoid cells and small lymphocytes were found to contain agglutinins, but only the former were capable of synthesizing antibody. The conclusion was deduced from experiments in which cultures were prepared from material in which the two types of cells were separated by sedimentation. The presence of great numbers of large, immature cells in the characteristic cell aggregates in the red pulp, together with the high agglutinin production found in this material, supported the hypothesis that the antibodies were being produced by the immature plasma cells of red pulp. The occurrence of immature lymphoid cells in white pulp where no plasma cells were found, together with an apparent production of agglutinin by this material *in vitro*, and an apparent agglutinin content of mature lymphocytes, suggested that lymphoblastic cells of Malpighian corpuscles were also involved in antibody production to some extent. The culture experiments seem to refute the idea of an antibody production by mature lymphocytes.

Transfer of cells from lymph nodes of sensitized or immunized animals is followed by a significant accumulation of antibody titer in the host animal. The synthesis of antibody evidently continues after transfer either in the transferred cells or newly excited in the host. The titers observed are beyond the range of those explainable on the basis of transference of preformed antibodies (33). A similar experience with regard to the development of antibody titers following the transference of splenic pulp cells is reported by Stavitsky (34), who also discusses the relationship between the route of injection and the differential activity of lymph node and spleen in production of antibody. The production of antibody in the spleen following intravenous injection of antigen far exceeded that observed in the lymph nodes. The evident importance of the spleen in man as a site of antibody formation (35) has been recently documented by Rowley (36), who demonstrated a failure of circulating antibody response in 13 out of 14 splenectomized individuals following intravenous injection of heterologous erythrocytes.

Cellular transfer of cutaneous sensitivity in man (37, 38, 39), as summarized by Lawrence (39), has led to the conclusion that the three classical types of skin reaction to antigen-antibody union, the delayed tuberculin type, the Arthus, and the wheal and erythema type, are all amenable to passive transfer independently by leucocytes. The transfer of cells to the negative recipient is, in effect, a transient endowment of the recipient with

qualitative versus quantitative effects be distinguished on the basis of tissue responses to immune reaction (18, 19). As an example may be cited the contentions of Kobernick *et al.* (20) who recently bring forward, contrary to some earlier opinions, (21, 22) the feeling that skin reactivity established by adjuvant usage in the case of foreign proteins is of the ordinary anaphylactic type and not a delayed tissue reaction of the tuberculin type. These workers feel that the differences in tissue reaction induced in rabbits by the use of Freund's adjuvant are distinguishable from the controls in which adjuvant is not used on purely quantitative grounds.

Antibody production—Focusing attention rather more upon constitutional variations in host antibody responses, and leaving aside for the moment the possibility that these variations may be predicated upon differences in antigen metabolism, Kuhns & Pappenheimer (23), in an interesting approach to the problem of allergy in general, present evidence correlating the production of a nonprecipitating type of antitoxin and an immediate wheel and erythema type of Shick reaction with an allergic personal or Shick family history. Their studies were carried out in a group of young adults receiving booster doses of purified toxoid and Schick skin tests, and the accuracy and simplicity of their system would appear to lead to further development (24). Conclusions, somewhat similar, concerning the importance of nonprecipitating antibodies in the establishment of skin sensitization, are contained in the studies of Sherman *et al.* (25), who were able to demonstrate in the passive sensitization of human skin by rabbit antiovalbumin, a maintenance of effect after removal of precipitating antibodies. They felt that the "univalent" antibody remaining after complete removal of precipitin by fractional addition of antigen showed an activity in passive sensitization of human skin equal to that of the original serum The difficulty of quantitative evaluation of skin reactivity is an inescapable hazard in work of this type, but Hanan (26) comes to similar conclusions concerning a lack of correlation between precipitability and ability to sensitize in studying the effect of ultraviolet radiation on the reactivity of antibody. In his experiments, the ability to produce passive anaphylaxis was reduced by a period of exposure to ultraviolet that left precipitin formation relatively unaffected.

Cellular changes associated with antibody production have received renewed attention partly because of the obvious effects of corticosteroids upon lymphoid tissue and upon hypersensitivity reactions (27, 28). McNeil (29) has described a definite progression of cellular hyperplasia in lymph nodes in rabbits after antigen injection. The order of progression of the cells producing the hyperplasia is neutrophile, lymphoblast, plasma cell, and finally large lymphocyte Antibody appeared in the serum coincident with the peak of plasma cell hyperplasia The role of these cells in the formation of antibodies has been further evaluated in tissue culture experiments by Keuning & van der Slikke (30). Rabbits were immunized by three intra-

was examined in fifteen patients with collagen diseases and in four with miscellaneous disorders The most frequently observed alteration was a reduction in serum γ-globulin as determined chemically. Less constant but still common was a reduction in plasma fibrinogen during treatment. Variations in responses were observed in volume of packed red cells, serum albumin, and serum mucoprotein. Total circulating protein components as estimated by concurrent plasma volume estimation in five cases were found frequently to change in an opposite direction to values expressed in amounts per 100 ml.

Until appropriate tracer techniques for studying protein synthesis and degradation are applied extensively to the determination of antibody half-life (50, 51, 52) in relevant pathologic states, the significance of changes in concentration alone in most clinical circumstances must remain somewhat equivocal. In the special case of the half-life of passive-acquired Rh antibody in new-born infants, however, it may be calculated that the half-life of the placenta-passing Rh antibody molecule is approximately 30 days, and evidence may be presented that this estimate applies not only to placenta-passing Rh antibodies, but also to other placenta-passing antibodies, and not improbably to serum γ-globulin molecules in general (53). Peculiarly, the studies on the fate of free Rh antibodies in erythroblastotic babies show that these antibodies often were eliminated no more rapidly in Rh-positive babies than in Rh-negative babies On the other hand, incompatible alpha and beta antibodies, as a rule, are quickly neutralized and eliminated from the body of newborn infants These observations provide one explanation for the lower incidence of erythroblastosis due to A-B sensitization in comparison to the incidence resulting from Rh sensitization

The general subject of the effect of x-rays upon the development of immunity has been recently reviewed by the Taliaferros (54). Development in this field has been accelerated by an interest in protecting animals from radiation injury of atomic or other origin. Jacobson *et al.* (55) have studied the effect of shielding the spleen during exposure to radiation and have demonstrated that ectopic blood formation is intensified in shielded spleens with recovery of the general hematopoietic system in about eight days. Animals whose spleens were not shielded from radiation damage failed to recover from the radiation injury. Somewhat similar observations in mice are reported by Kaplan (56) and Lorenz (57), who found that peripheral shielding appeared to facilitate recovery of lymphoid tissue Jacobson (58) also demonstrated that the capacity to form antibodies to an injected antigen is retained in rabbits exposed to 500 to 800 r total body x-radiation if the spleen was shielded during irradiation, left intact in the circulation 24 hr after irradiation, and then removed surgically, even though the antigen was given 24 hr before splenectomy and 48 hr. after irradiation. The fact that these rabbits retained the capacity to form antibodies, even though hematopoietic tissue in the body was atrophic, and that control rabbits exposed

an apparatus capable of responding with specific reactions usually possible only as a result of specific sensitization

A general distinction between two phases of antibody response has been achieved by studies with irradiated animals. Dixon *et al.* (40) and Kohn (41) and Taliaferro & Taliaferro (42) have showed that irradiation before injection of antigen causes a marked suppression of antibody formation Irradiation shortly after administration of antigen does not, in the dosage used, interfere significantly with antibody production. Similarly, irradiation before a stimulus calculated to awake an anamnestic reaction did not prevent the usual antibody response. The significance of these observations as indicative of the importance of the time of application of the restraining influence might be borne in mind in considering some of the peculiarities of antibody response that have been described in connection with the use of cortisone and ACTH.[2] Incidentally, it may be recalled that neither cortisone (43) nor x-ray radiation (44) in dosage of 300 r affect the rate of destruction of passively transferred homologous and heterologous antiserum intravenously administered in rabbits. This amount of x-ray was, however, sufficient to decrease, but not totally prevent, the production of antibody to heterologous serum protein. A similar amount was found to depress the Arthus reaction (45), probably because of its effect upon antibody titer.

The lack of correlation between antibody production and various other disturbances of protein metabolism was studied by Larson *et al.* (46) using pneumococcus type 1 and type 2 specific polysaccharides as the antigenic stimuli. In 12 patients with abnormal levels of serum protein, there did not appear to be a relationship between total serum protein, total serum albumin, total serum globulins, total serum euglobulins, the electrophoretic pattern, and the ability to form antibodies. In the patients studied, the ability to maintain elevated total serum globulins bore no apparent relation to the ability to produce antibody globulin. Four patients with cirrhosis of the liver had normal antibody responses Four patients with multiple myeloma and high globulin levels had notably poor antibody responses and unusually low titers of C antibody. On the other hand, Rantz *et al.* (47) were impressed by the immunologic hyper-reactivity of a group of patients with rheumatic disease, and felt that their hyper-reactivity was of importance in the pathogenesis of their diseases. Evans & Rackemann (48) are evidently of similar opinion.

In interpreting the meaning of changes in antibody concentration, it is difficult to distinguish between possible changes in rates of destruction, changes in rates of formation, and possible expansions in antibody space Jager and associates (49) have shown that in studies of the effect of ACTH[2] or cortisone upon antibody levels, consideration of the effect of expansion of the extracellular fluid space may alter conclusions regarding the significance of observed changes in γ-globulin concentration. The effect of ACTH or cortisone upon volume of packed red cells and plasma protein components

or passive anaphylactic shock. Treatment with the hormone during the period of active sensitization diminished the intensity of the Arthus reaction and the quantity of circulating antibody produced. Neither of these effects was as great as that observed in rabbits following the administration of comparatively smaller doses of cortisone. Similarly, the anatomic protection afforded by cortisone was less striking in the guinea pig than in the rabbit. The findings suggest that the guinea pig is more resistant to the action of cortisone or more susceptible to anaphylaxis than is the rabbit. The failure of cortisone to abolish the active Arthus reaction and its failure to alter active anaphylactic shock was probably related to the incomplete suppression of circulating antibody in the experimental conditions employed.

Baker, Ingle & Li (68) have reported the effect of ACTH[1] upon the lymph organs of rats, and Craig (69) has made a careful study in rabbits. Rabbits receiving adrenocorticotropic hormone or cortisone during the period of maximal antibody production caused by a single antigenic stimulus showed a significant depression of the normal histologic response in the affected regional lymph nodes. The repressive influence was found in the reduced mass of the affected lymph nodes, in their narrowed cortex, in their lack of reaction centers, and in the partial inhibition of the formation of germinal centers and mitotic figures.

The action of cortisone and ACTH in alleviating many of the symptoms of hypersensitivity has seemed to require an explanation beyond the rather minor change induced in antibody concentration As an alternative, a major aspect of the hypersensitivity reaction, the change in permeability induced in vasculature, in cells, and in general extracellular supporting structure, might be here considered. Aikawa *et al.* have demonstrated an expansion of the thiocyanate space in several examples of hypersensitive response: trichinosis (70), serum sickness (71), and passive anaphylaxis (72). The time of occurrence of the expansion coincides with the time of development of circulating antibody and the outbreak of symptoms. Because of an associated drop in blood volume, the increase in extracellular space is believed to indicate an alteration in vascular permeability and a generalized edema at the time of allergic reaction. The reports of Longcope & Rackemann of chloride retention and edema during serum sickness in man are doubtless earlier, more familiar examples of the same phenomenon (73). The local edema of the Arthus reaction and the wheal and erythema of positive skin testing are local counterparts, all being changes in barrier permeabilities induced by antigen-antibody combinations The mechanism of these events is not known, but interest centers as usual in possible alterations in polysaccharide ground substance (74). The fibrinoid swelling and collagen disintegration observed in severe lesions lacks chemical definition (75), but electron microscopy of rheumatoid tissue and normal and diseased collagen (76, 77, 78) has brought at least a recognition of the normal and an understanding of some of the factors involved in the fibrogenesis of collagen. The

to 500 to 800 r did not retain this capacity, was considered to be a result of the functional restoration of cells in the body (such as free and fixed macrophages and reticular cells) by a humoral (noncellular) substance entering the general circulation from the originally shielded spleen during the twenty hours prior to splenectomy.

Action of ACTH and Cortisone

A host of studies of the effect of ACTH[2] and cortisone upon blood antibody concentrations has appeared. It seems apparent that administration of these compounds to immune animals in general results in very little change in the concentration of circulating antibody. Hammond *et al.* (59) were able to confirm the earlier experiments of Dougherty and co-workers (60) showing a rise in hemolysin titer in immune rabbits upon the injection of lipo-adrenal extract. They were not, however, able to demonstrate that the mechanism of this rise was the release of antibody by circulating lymphocytes. Havens *et al.* (61) could show little effect upon the production or decline of antibody titers when the adrenal compounds were given after administration of antigen. De Vries (62) could show no rise in antibody titer following the administration of adrenocorticotropic hormone in animals immunized to egg albumin. Bjørneboe, Fischel & Stoerk (63) found that cortisone and ACTH caused a drop in antipneumococcus titers when given either at the beginning of immunization or after immunization has well started. In patients with rheumatic disease, ACTH and cortisone depressed the concentrations of gamma globulin and fibrinogen (64). One is reminded of Jager *et al.* (49) on the importance of volume changes in interpreting changes in antibody levels, and of the additional possibility that increments in concentration from lysis of cells containing antibody may be offset by a decreased production in the active lymphoid centers as a consequence of the hypoplasia induced by the hormones. The study by Tillotsen (65) of the effect of cortisone on the Arthus phenomenon as related to the time of sensitization is pertinent. Cortisone given to rabbits during active sensitization decreased antibody formation, reduced the amount of exudate, and prevented the vascular necrosis of the Arthus reaction. Cortisone given to rabbits after sensitization did not affect antibody titer or the vascular necrosis of the Arthus reaction, but did reduce the amount of exudate. Short courses of cortisone produced slight atrophy of lymphoid tissue, whereas longer courses produced atrophy of bone marrow, atrophy of the peripheral cortex of the adrenal, and decrease of the granules in the beta cells of the pituitary.

Germuth *et al.* (66, 67) have made careful studies of the effect of cortisone upon the development of experimental hypersensitivity and circulating antibody titers in the guinea pig and rabbit. In the guinea pig, somewhat less depression of antibody titers and anaphylaxis was observed than in rabbits. Large doses of cortisone failed to protect guinea pigs against active

reversible, and after treatment was stopped an exacerbation of the vascular changes was observed. It was felt that cortisone produced a profound effect on the integrity and reactivity of small vessels, and that the suppression of the *in vivo* manifestations of serum disease was a result of this nonspecific effect rather than of a suppression of antibody formation or antibody-antigen union.

The changes in vascular permeability induced by immune reactions have their cellular counterparts in changes in cell permeability (87) that are perhaps most easily seen in the lysis of erythrocytes, though leucocytes (87), platelets (88), and other cells perhaps share the phenomenon. The demonstration by Fisher & Keogh (89) that lysis may be accomplished, in the presence of complement, in the case of erythrocytes which have adsorbed a nonerythrocytic bacterial component and its antibody is of extreme interest. The observation has been confirmed (90) and its generality extended by Adler (91) to include bactericidal action mediated by antibodies specific for heterologous antigens adsorbed to bacterial cells. The mechanism of the lysis remains unclear but its demonstration is important in that it indicates that cells may be damaged by immune reactions occurring on their surfaces although these surfaces are innocent of participation in the actual antigen-antibody reaction As an approach to the meaning of these observations, a number of studies defining more clearly the nature of the red cell membrane, its receptor sites, and the changes induced by lysis (92 to 97) have been presented.

Unfortunately evidence of an action of cortisone protective to cell permeability in general does not appear forthcoming Erythrocytes lyse, white cells and platelets disintegrate, and histamine is released (98, 99) despite treatment with the hormone (85, 86) Possibly careful titration of the immune systems in minimal concentration might alter this conclusion, but in animals such as the guinea pig, whose bronchi are markedly sensitive to histamine, it is difficult to show over-all protection from hormonal treatment (100 to 103). Quantitative evaluation justifies the conclusion that a measure of protection is afforded (66, 104), some organs showing protection (105 to 108) against histamine-induced spasm more readily than others, and the inhibition of edema in the sensitive bronchi (104) again demonstrating the importance of the effects upon capillary permeability.

It was demonstrated by Dougherty & Schneebeli (109) that cortisone inhibited allergic inflammation through an antiphlogistic action rather than by interfering with the antigen-antibody union Subsequent observations have confirmed the reasonableness of his contention (110 to 113). Ebert's (85, 86) observations of a diminished diapedesis of white cells and the observation that treatment with ACTH and cortisone lessens the bleeding of thrombocytopenic purpura by a decrease in capillary fragility (114, 115) affords one type of explanation for the results obtained The early protective effect of the hormone limits capillary damage and prevents the escape of

observations of Gross *et al.* (79) are pertinent in showing that the *in vitro* genesis of collagen fibrils of both normal and long-spaced periodicity may be affected by the nonspecific action of a number of factors, such as ionic strength, hyaluronate, chondroitin sulphate, and heparin, but more importantly, by the peculiar activity of an unknown material extractible from fibrous tissue, and perhaps particularly the carbohydrate moiety thereof.

The general inhibition of changes in permeability of immune origin by cortisone constitutes one of the most significant actions of the hormone The mechanism is hidden (80) but its application is generic, counteracting a wide variety of stimuli. Thus following Opsahl (81), Ducommun *et al.* (82) observed that the spreading of subcutaneous injections of hemoglobin, induced by lyophilized anterior pituitary, somatotropin and desoxycorticosterone was inhibited by cortisone. Chappell *et al.* (83) in studying the cutaneous histamine response of rabbits using Evans blue dye as an indicator, found that cortisone inhibited the histamine induced change in capillary permeability and limited the diffusion of dye. The influence of ACTH[3] and cortisone upon the alteration in capillary permeability induced by hyaluronidase in rats was studied by Benditt *et al.* (84). Intravenous administration of 2000 units of partially purified testicular hyaluronidase in rats caused an increased rate of disappearance of Evans blue, a decreased concentration of serum protein, and an increased hematocrit. These manifestations of an increased capillary permeability due to the action of the enzyme preparation were largely inhibited by five days pretreatment with subcutaneous administration (5 mg. per day) of either ACTH or cortisone acetate. A minimum of 24 to 48 hr. of pretreatment with cortisone acetate was required for a discernible inhibition of the hyaluronidase effect. The evidence suggests an intermediate step between cortisone acetate and its action on connective tissue.

In vivo observation of the effects of cortisone on the vascular reaction to large doses of horse serum has been made by Ebert & Wissler (85, 86). As observed by the ear chamber technique in rabbits, cortisone produced a quantitative reduction in the *in vivo* manifestations of serum disease. Treatment reduced the evidence of vascular damage: vascular tone was better maintained, vascular endothelium tended to keep its normal refractile appearance, swelling of endothelium was suppressed, and there was reduction in the sticking of leucocytes to endothelium. Sludging of erythrocytes was less marked, and platelet and white blood cell thrombi and emboli were less numerous in treated animals, but the suppression of these intravascular changes was less dramatic than the reduction of vascular damage As a result of the increased integrity of vascular endothelium, there was decrease in diapedesis of leucocytes and a reduction in the accumulation of exudate. There was also a reduction in the systemic reaction following the second injection of horse serum in treated animals. The effects of cortisone were

reversible, and after treatment was stopped an exacerbation of the vascular changes was observed. It was felt that cortisone produced a profound effect on the integrity and reactivity of small vessels, and that the suppression of the *in vivo* manifestations of serum disease was a result of this nonspecific effect rather than of a suppression of antibody formation or antibody-antigen union.

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formed elements from the blood at the site of inflammatory injury. Examples of this protective action through the lessening of edema, exudate, and necrosis in the early stages can be seen in most of the studies of the Arthus phenomenon (67, 116 to 119), the Schwartzmann reaction (120 to 124), the serum-induced periarteritis. (125, 126, 127). The end result is not wholly benign. The late occurrence of necrosis appears to be increased in extent (128 to 131) particularly, perhaps, in renal tissue. Rich *et al.* (130) found in their experimental animals that cortisone and ACTH inhibited the development of proliferative glomerular lesions, but cortisone induced a severe glomerular damage with accentuated hemorrhage reminiscent of acute hemorrhagic glomerulonephritis in man. In other work (131) bilateral cortical necrosis of kidneys occurred in cortisone-treated rabbits following the injection of bacterial toxins. These observations call to mind the generic inhibition of mesenchymal repair perhaps first brought forward by Ragan (132, 133), but now much extended (134 to 142), and serve to introduce a group of references (143 to 158) all tending to attest the disadvantageous action of cortisone in the presence of infection. In these latter cases, aside from the mystic beneficial effect upon fever (159) and toxemia (160, 161), the hormone by its inhibition of local inflammatory response, rather than by any great interference with phagocytosis *per se* (144, 162), seems to favor markedly the spread and extension of the infectious agent. Thus in tuberculosis the delayed skin reaction to tuberculin is inhibited (163 to 167), as might be expected from the action of the hormone in reducing inflammatory response, but the dissemination of infection and the progress of the disease is accelerated (168, 169).

Clinical Allergy

Clinical investigation of allergy recently has centered in studies of the application and action of ACTH and cortisone. The general metabolic effect of these hormones has been well reviewed (170, 171, 172), their potentialities for producing hypertensions, diabetes, disturbances of psyche (173), and other abnormalities (174 to 179) have become common knowledge. Methods of administration and dosage schedules to conform to various needs and circumstances have been elaborated. In general, it may be said that clinical results are gratifying, but since neither hormone strikes at the heart of the allergic process, and since each induces atrophic changes in the corresponding host gland, in addition to augmenting extension of the oft associated infection, there is little of the physiologic (180, 181) or etiologic in their application. Used with antibiotics, they may be most helpful in lessening the acute inflammations, edemas, and spasms of the allergic process; their prolonged use is hazardous; their repeated use is better (182). There still remains the hard core of allergic management: avoidance of allergen, local surgical hygiene, desensitization, and general medical and psychologic support (183). As for modes of administration, in the average hospital prac-

tice with severely ill patients, there is much to be said for the efficacy, economy, and rapidity of action of slow intravenous infusion of ACTH (184 to 187). For out-patient and office work, other routes and longer acting preparations (188, 189) have their advantages, and in many instances the ambulatory patient is handled most conveniently on a schedule of oral cortisone (190). Efforts to stimulate significant endogenous ACTH release by prolonged administration of epinephrine (191) or other drug (192) and searches for less expensive but similarly acting compounds have not met with success (193).

The clinical application of ACTH and cortisone to the treatment of allergic disease has been extensively reported and reviewed (48, 194 to 200). The review by Evans & Rackemann (48) is particularly helpful. In asthma most observers report improvement, variously ascribed to a relaxation of spasm and a reduction in bronchiolar edema and cellular infiltration. There is, in addition, a general betterment of metabolic and psychological state, return of appetite, gain in weight, and increase of morale. Relapses on discontinuance of therapy continue to be discouragingly frequent and prompt, unless treatment coincides with effective removal of the allergen or eradication of concomitant infection by administration of antibiotics (48, 201 to 207). Deaths from asthma continue to occur (48) in all age groups but particularly in patients whose asthma begins in middle life or later, the intrinsic or bacterial variety being the most dangerous (208, 219). Inadequate pulmonary ventilation, detectible in most asthmatics, even in their symptom-free periods (210), and easily demonstrated by an inhalant test with the specific allergen (211), would appear to be the chief cause of fatality, with cor pulmonale and periarteritic lesions as frequent consequential complications

In allergy of the upper respiratory tract (212, 213, 214) the usual prob-problem of evaluating the usefulness of surgery continues (215, 216). Obvious foci of poorly draining infection should be given mechanical treatment but the more subtle improvement of spatial relationships that can be achieved by reduction in lymphoid tissue through x-ray (217) or endocrine therapy (218, 219), particularly in children, is much to be preferred. The symptoms of hay fever and the bronchial asthma often associated with it are both well-relieved by cortisone and ACTH (220, 221). Skin reactions to the antigens are not however, significantly affected, and quantitative studies of the ophthalmic and nasal reactions in patients with nasal and conjunctival allergy have shown these reactions not to be greatly altered (222, 223). Sensitizing antibodies as a rule remained unaffected by treatment (224, 225). It is probable that these simple titration tests are inadequate to detect minor changes that may be of significance in a lower grade, continuous type of elicitation, more nearly duplicative of the natural disease. The impression remains, however, that hyposensitization is useful (225) and that the hormones diminish the patient's reactivity to the allergic stimulus, chiefly by

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Interest in histamine metabolism, histamine, and antihistaminics (287) has been perhaps less general during the current period of preoccupation with cortisone and ACTH. The clinical usefulness of antihistaminics (288, 289, 290) continues, though certainly not as a treatment for a common cold (291 to 294). Evidence of a possible interrelation of histamine metabolism (295) and cortisone effect has appeared (296, 297, 298), but the observations do not establish this connection as a major explanation of the clinical action of the hormone.

reducing edema, swelling, and cellular infiltration rather than by producing basic change in the allergic constitution.

The generic antipholgistic effects of the hormones continue to explain their usefulness in the management of diseases of the eye (226 to 229) and of the skin (230 to 234) and of the vasculature (235 to 238), and the probable reasonableness of their trial in certain types of neurologic disease (239 to 243). A similar statement might perhaps be made in regard to rheumatic fever where the symptomatic relief (244, 245, 246), including the disappearance of signs of heart failure, is most satisfying but where the specific tissue changes persist (247, 248), and death and continued heart damage are not (249, 250) always avoided.

The increasing availability and usefulness of viral and rickettsial vaccines prepared from cultures grown on chick embryos has given significance to the question of the production of sensitivity to egg proteins by intradermal and subcutaneous injection of these vaccines. The review by Ratner *et al.* (251) indicates that the hazard is not numerically important probably because of a general resistance to egg sensitization acquired as a consequence of the popular habitual ingestion of eggs and egg-containing foods. Patients with known egg allergies should continue to be cautious in the use of these vaccines. Allergies to eggs and to certain other foods (252 to 255) may be demonstrated by roentgen studies of the upper gastro-intestinal tract (256, 257). Treatment with cortisone or corticotropin appears helpful (258), but avoidance of the allergen is to be preferred.

The effect of cortisone and ACTH upon various disorders of the blood has been well documented (258, 259). Aside from the effect upon eosinophiles, the exact mechanism of which seems to be receiving further attention (260 to 268), interest to the allergist centers in those conditions of known or presumed immune etiology. Acquired hemolytic anemia, particularly cases showing a positive Coombs test, in general seems to respond favorably to hormonal treatment (269, 270, 271), a concomitant drop in agglutinin titer and Coombs reaction usually being observed (269). The hypersensitive origin of thrombocytopenic purpura is perhaps less well demonstrated (272, 273), but the clinical results of treatment appear equally gratifying (274, 275, 276) perhaps in part because of an additional factor of improvement in capillary fragility (114), and a direct effect upon blood coagulation itself (277 to 280). Unfortunately, aside from the benefit attendant upon these latter two nonspecific effects, treatment with hormone does not appear to alter the final outcome of cases of aplastic anemia of chloramphenicol origin (281 to 285) The symptomatic relief afforded these and other patients in similar circumstances from agranulocytosis, leukemia, etc does appear however to justify their treatment with either ACTH[2] or cortisone. The exudative, toxic, pyretic, and hemorrhagic phenomena of drug hypersensitivity in general seem most satisfactorily alleviated by this form of treatment (286), and the secondary infectious processes do not appear to go out of control provided suitable antibiotics are employed.

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NEOPLASTIC DISEASES: SOME METABOLIC ASPECTS[1]

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Effective control of any disease requires that its medical, social, and economic significance be minimized by practical prevention or adequate treatment. Either modality necessitates the continuing accumulation of factual data until the entity is so well understood that the answer sought for becomes apparent. Cancer is not a single disease. Common denominators do exist among malignant neoplasms, however, encouraging the investigator in the belief that general principles established from the study of experimental cancers may be extended to the clinical situation. Extrapolation of data from lower animals to man is fraught with many pitfalls The genetic approach to the study of experimental carcinogenesis, for example, has contributed much to our knowledge of the etiology of cancer in mice but the techniques have required intensive inbreeding by brother to sister mating for many generations, whereas the human population is necessarily hybrid. The concept of commonality of cancerous tissues rests partly on Warburg's characterization of a common, though not pathognomonic, type of metabolism among malignant tumors (1), Greenstein's observation that neoplasms tend to converge enzymatically to a common type of tissue (2), and Roberts' & Frankel's finding (3) of a more uniform pattern of extractable amino acids from cancers than from their tissues of origin. Only Warburg's thesis has been tested extensively and affirmed at the clinical level Certain practical difficulties impede some chemical investigations of clinical cancers Anesthesia and arrest of hemorrhage necessary to definitive surgery, whence stems material for analysis, may alter the composition of the sample (4). The rigid control necessary to precise definition under laboratory conditions is seldom achieved in clinical investigations of cancer, yet clinical investigators seem to understand dynamic interrelationships of the cancerous state better than do most of those who work in the so-called basic sciences The laboratory is far ahead of the clinic in studying many important aspects of the cancerous state The gap is difficult to close.

The Act of Congress in 1937 which created the National Cancer Institute gave great impetus to the study of neoplastic diseases The direction which cancer research might reasonably take was investigated by a committee of eminent students of cancer (5). They held that effective control of malignant neoplasms might be achieved from study of these major facets: (*a*)The causal genesis—the proximate causes of cancer, both intrinsic and extrinsic; (*b*) The formal genesis—the basic mechanisms responsible for the transforma-

[1] The survey of literature pertaining to this review was completed in September, 1952

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The concept of anaplasia as dedifferentiation of adult cells or reversion in the direction of the embryonal state established by morphologists finds considerable support in the biochemists' comparative analyses of cancerous, adult, and embryonal cells of common histogenesis. The failure thus far to find discrete qualitative differences among the three types of cell eliminates for the present one rational approach to the better management of clinical cancer through drug action.

Metabolic Aspects of Chemotherapy

The empirical method of testing multitudes of compounds against experimental cancers and gingerly attempting to reproduce in man such beneficial effects as may be observed has led to the discovery of several compounds which seem to be useful in the management of some forms of clinical cancer. None of these agents is curative Some of them have focused attention on certain biological processes and, indeed, have furthered our knowledge of intermediary metabolism

Currently available data suggest that the antifolic compounds interfere with synthesis of nucleoprotein by preventing the donation of carbon derived from formate to the purine ring (9) The ability of antifolics administered by conventional routes to affect the course of leukemias, as contrasted with their relatively negligible effect on epithelial neoplasms in general, may reflect in some measure the character of the cells from which these two large neoplastic groups originate. One might expect, on teleological grounds, that the cells derived from tissues most actively concerned with synthesis of nucleoprotein would be those most susceptible to the action of antimetabolites that prevented its formation. The evidence indicates that the rate of formation of nucleoproteins is higher among hematopoietic tissues and the mucosal cells of the small intestine than in most other sites under ordinary circumstances Thus we find the course of some leukemias interrupted by nucleoprotein antimetabolites but their usefulness is limited by untoward effects on the intestinal canal This rationalization is oversimplified. Some leukemic cells may actually use certain antifolic compounds in such a way that they become dependent upon them for maintenance of their integrity (10) Other leukemias resist the action of the drugs completely, for no obvious reason

The complexity of the situation may be illustrated further by recounting briefly experience with another antimetabolite of nucleoprotein synthesis, 8-azaguanine This interesting compound arrests the development of certain transplantable tumors that grow in mice but is largely ineffective when tested against comparable anatomical types of neoplasms in rats (11). The rat prefers to synthesize nucleic acids from adenine One would expect 8-azaguanine to interfere with reactions involving guanine much more effectively than those principally concerning adenine, hence differences in the use of these purines in nucleic acid synthesis might be anticipated (12, 13) Hirschberg, Kream & Gellhorn (14) found, however, that 8-azaguanine was

tion of the normal cell to the cancerous state; (c) Therapeusis of cancer—extension of already existing methods and development of new ones, particularly cancerocidal drugs.

These are the general directions that cancer research has taken throughout the world. Some progress has been made.

Etiology

Two basic principles of the etiology of cancer were established long ago by the astute observations of Percival Pott, who found that cancer may be caused by an external stimulus which takes a long time to produce its effect and will not necessarily provoke cancerous change in all the members of a population (6). These fundamentals have been confirmed repeatedly in animal studies and in that small segment of clinical cancers that result from occupational hazards. Ancestry apparently influences one's risk of cancer, for strong genetic factors may modify the individual's response to cancer-producing stimuli which may be of exogenous origin or produced, perhaps, by the body's own cells Geneticists recognize that hereditary factors must be defined physiologically or, better, in terms of chemistry and physics before they may be useful in the practical control of cancer. Progress in this direction depends in large measure on better understanding of the minutiae of metabolic processes The large number of diverse agents that may elicit malignant neoplasms, the complexity of factors that influence their action, and the wide variation in types of both experimental and clinical cancers discourage the thought that practical prevention of the generality of malignant neoplasms will be attained in the foreseeable future.

Some workers have postulated that filterable viruses cause all cancers The viral etiology of some tumors in lower animals is established but no incontrovertible evidence has yet been adduced that would incriminate a filterable virus as a major factor in the production of any malignant neoplasm that affects man. Current information, indeed, suggests that the agent transmitted from mouse to mouse that influences importantly the incidence of mammary tumors in the females of the species is not a prerequisite for development of cancer of the breast. The lesion may develop in mice in which the mammary tumor inciter cannot be demonstrated (7)

It is conceivable that one fundamental process is common to all transformations of normal to neoplastic. University of Wisconsin scientists (8) have speculated that carcinogenic agents may damage key intracellular proteins "essential for the control of growth but not for the life of the cell." The damage could in some way prevent or hinder synthesis of some proteins, or induce the synthesis of altered proteins whereby cell generations might arise that lacked one or more regulators of growth This hypothesis is supported by the study of experimental carcinogenesis in the liver and epidermis with different chemical agents both of which produce protein carcinogen complexes Much more work is required but the theory could account for the wide diversity of agents that can evoke cancer.

the growing cancer remains localized and does not seriously interfere with bodily functions for purely anatomical reasons. Study of such a system reveals that the total mass of a cancerous rat increases at approximately the same rate as does the weight of the noncancerous rat of same age, sex, and initial weight when each subject eats freely a semi-synthetic diet adequate for growth, pregnancy and lactation (15). Variation in weight increment is great, however, and the death of the tumor bearer is preceded by a brief period of rapid weight loss. The food intake of the two subjects is quite different The normal rat eats well. The cancerous host loses its appetite. Anorexia does not coincide with the onset of tumor growth but commences at a critical point in the evolution of the lesion and is largely progressive thereafter. The critical point in rats that weigh 200 to 250 gm and bear Walker carcinoma 256 is reached when the growing neoplasm forms about 10 per cent of the total body weight (rat and tumor). The apparent paradox of equal growth rate, despite wide discrepancy in food intake, reflects in some measure the great water content of the neoplasm as compared with normal tissues. It is essential then to study normal and cancerous subjects which ingest identical amounts of the same diet, if the results of metabolic investigation are to be meaningful. This may be accomplished by paired feeding, in which the normal rat is fed the precise amount of the diet eaten by its cancerous fellow, or by gavage. Both subjects must be of the same age, weight, and sex at the beginning of the study and their growth rates must have been established to be comparable

The noncancerous rat that eats identical amounts of the same diet ingested by a rat bearing a cancer fails to gain weight shortly after the tumor has commenced to grow in the cancerous host, and ultimately loses weight if the food intake is expressed in terms related to the weight of the experimental animal (15). Paired feeding on an absolute basis permits the tumor-free rat to gain or lose weight more slowly than does the tumor bearer (16) One may calculate the weight of the growing tumor satisfactorily *in vivo* (17) which permits analysis of weight changes in terms of tumor and host This procedure indicates that the Walker tumor has three different stages of growth A tiny mass becomes palpable at the site of implantation 7 to 10 days after a piece of tumor has been transplanted aseptically to subcutaneous tissues It grows slowly but progressively and the body gains weight at the same time The second phase is characterized by much more rapid neoplastic growth while the host tissues lose weight. The onset of anorexia appears to coincide with the beginning of this period. The subject may die during this stage of tumor growth, but many cancerous rats pass into a final brief phase during which the tumor grows slowly, if at all, (partial regressions have been noted), and the rate at which the host's tissues lose weight is markedly accelerated. Pair-fed cancerous and noncancerous rats usually excreted almost identical amounts of nitrogen during the first two stages of tumor growth (18). An occasional cancerous subject, however, appeared to store more nitrogen than did the noncancerous pair-fed control. The last

converted to azaxanthine by homogenates of some normal and neoplastic tissues. The latter compound has no carcinostatic power. Azaguanine deaminase activity was high in three azaguanine-resistant tumors, low in three of the four azaguanine-susceptible neoplasms tested Liver detoxified the drug rapidly in any case, which would necessarily provide progressively diminishing amounts of the agent for inhibition of cancerous growth. They also presented some evidence that a similar mechanism operates in the intact animal. Perhaps the relative efficiency of nitrogen mustards in interrupting progressive growth of certain solid tumors when given by the intra-arterial route as compared to intravenous injection is the result of a comparable phenomenon or is a function of the concentration of the drug delivered to the tumor.

The empirical approach to the chemotherapy of cancer is not only necessary until some better approach can be developed but also contributes much fundamental information that advances our knowledge of physiology, pharmacology, and biochemistry. It must be continued even though it requires the utmost in diligence, patience and constant re-evaluation of methodology.

Nutritional Aspects of Cancer

More precise definition of the tumor-host relationship may provide both a rational basis for affecting cancerous growth through drug therapy and some means of improving current management of clinical cancers. A neoplasm participates in the economy of its host A dynamic equilibrium between cancerous and noncancerous tissue must exist in each individual, which will be determined largely by the growth vigor of the neoplastic cells and their concentration within the body. The patient with a small localized cancer frequently presents no other obvious abnormality, but the same subject often appears markedly different even to casual inspection when the neoplasm has become disseminated, although the cancerous cells may have produced no lesion which might have interfered with bodily functions solely because of their anatomical relationships. Ulceration of a surface with exsanguinating hemorrhage or overwhelming sepsis, obstruction of a viscus or essential excretory pathway are incompatible with health and indeed with survival, regardless of their etiology Cancer may produce such effects but it is perfectly capable of bringing about deterioration of the host through alterations in the physiological status of its victims There is no reason to believe that each malignant neoplasm mediates its deleterious effects in the same way, but certain common mechanisms should be sought for and defined in terms of pathological physiology.

The principal constituent of most tumor cells other than water seems to be protein. Nitrogen metabolism reflects protein synthesis and degradation in some measure and may [illegible] index of protein metabolism. What [illegible] blocks for cancer cells? [illegible] extent on the stage to which the cancer has developed. It can best be studied in animals bearing transplanted neoplasms in some region of the body where

mately 20 to 24 per cent of total body weight (rat and tumor) when the rats were sacrificed, whereas free-fed rats will grow Walker tumors that constitute 40 per cent of the total The workers confined their experiments then to one segment of tumor growth and prevented weight loss during that period. They also observed a greater retention of nitrogen, sodium, and chloride in the cancerous subjects

Stewart (25), working in Begg's laboratory, extended these observations by feeding Ingle's high carbohydrate, high fat, or high protein diets (26) to groups of rats that weighed approximately 200 gm. when the tumors commenced to grow. Each animal received 70 calories per day. The experiments were terminated when the neoplasms had attained a mass approximating 25 per cent of the whole. The carcasses weighed slightly less than did the bodies of noncancerous control rats Carcass weight loss was not prevented Stewart thought that the caloric intake was more important in determining the effects of diets on weight changes in the cancerous host than was the composition of the ration, providing the dietary ingredients were qualitatively adequate for growth of normal rats One striking difference in the reaction of the rats to the various regimens, however, dictated the experimental design, for Stewart, as had Begg and Dickinson, found that rats bearing the Walker carcinoma could not tolerate indefinite administration of the high fat diet at a level of 70 calories daily Normal rats handle the ration with no apparent difficulty, but tumor bearers develop a profound metabolic disturbance characterized by hyperlipemia of monumental proportions when the tumor weight approaches 25 per cent of the whole rat.

The situation has been studied at Rochester and appears to be entirely analogous to that observed by the Canadian investigators The rats develop hematuria Their blood has the color of brick dust and centrifugation yields an opaque white plasma indistinguishable from cream Bloor & Haven found that the concentration of lipids in such plasma exceeded 5 per cent, principally because of enormous increase in the saponifiable fraction (27) Structural changes in the kidneys of such cancerous subjects were similar to those usually ascribed to choline deficiency in weanling rats Intracellular sudanophilic globules were demonstrated in the nephrons The kidneys of normal rats that were fed the same amount of the same diet revealed no pathological changes The mechanism of this peculiar reaction can be elucidated only by further study but it does suggest that the nutritional requirements of the cancerous rat may differ from those of the noncancerous rat

A medium carbohydrate diet (28) was fed at a level of 70 calories daily by gavage to rats bearing Walker carcinoma 256 The limiting factor in tumor growth was ulceration Loss of weight from the carcass was prevented when the neoplasms constituted about 25 per cent of body weight but was not prevented when tumor weight approximated 30 per cent of the whole The cancerous subjects stored more nitrogen, potassium, sodium, and phosphorus than did the control rats Certainly tube feeding permits the cancerous host to grow a larger tumor in absolute terms without carcass weight

stage of growth of the Walker tumor was characterized by excessive excretion of ammonia and urea in the urine of the tumor bearers.

Total weight loss from non-neoplastic organs and tissues of cancerous subjects uniformly exceeded that lost by the relatively normal pair-fed rats The carcasses (rat minus tumor) of the cancerous hosts contained less nitrogen than did the bodies of the pair-fed controls, but when the nitrogen contained in the tumor was added to carcass nitrogen the total nitrogen in the pair-fed cancerous and noncancerous rats was not significantly different. Nitrogen balance studies in rats bearing Walker carcinoma 256 or Murphy-Sturm lymphoma showed that the neoplasms contained more nitrogen than was stored by their hosts during the period of tumor growth (15). These data indicate, then, that some cancerous rats break down normal protoplasm to provide building blocks for neoplastic tissues (19) This is a net result. It does not reflect the processes of intermediary metabolism that are involved. It does indicate that the diet's contribution to the "metabolic pool" of nitrogen may be inadequate to meet the continued demands of both normal and cancerous tissues. Anorexia is doubtless a major contributing factor.

Translocation of nitrogen from body tissues to neoplasm is accompanied by a progressive loss of total body lipid, principally at the expense of fats and fatty acids (18). It exceeds the amount of lipid lost from bodies of pair-fed noncancerous rats (20). A tendency for rats bearing Walker carcinoma 256 to hoard unsaturated and burn saturated fatty acids has been found by Haven, Bloor & Randall (21) It has also been shown that the concentration of total lipid in the tumor may fall as the cancer grows larger if the diet contains relatively small amounts of fat (15). The concentration of total lipid in the neoplastic tissue is maintained at a reasonably constant level when fat provides the major portion of the ration ingested by the subject (16). In any case, the second phase of tumor growth is accompanied by hyperlipemia which later tends to disappear as body lipids become depleted (23). Perhaps the increased excretion of nitrogen during the third period of tumor growth results from the loss of body fats. The subject then has little or no appetite Energy demands must be met by burning body substances. No known mechanism exists by which the rat may store enough carbohydrate to tide it over a period of comparative starvation Fat provides the major fuel reserve and, if this be depleted, the only recourse is to degrade protein, deaminate the amino acids, burn the carbon residues and excrete the amino groups as urea and ammonia. Excessive loss of lipid suggests increased energy expenditure by cancerous subjects (20, 24)

Study of rats bearing Walker carcinoma in which anorexia was circumvented by tube feeding has provided certain data which seem to contradict the hypotheses developed from the observations of pair-fed subjects Begg & Dickinson (23) provided a daily intake of approximately 70 calories to 4 rats weighing 150 gm at the inception of tumor growth. The cancers grew progressively and normal tissues gained as much weight as did the bodies of noncancerous rats of the same initial weight. The tumors weighed approxi-

losing weight. Others gained far more weight than could be explained by the conversion of nitrogenous substances to body protoplasm on the assumption that retention of approximately 30 gm. of nitrogen should increase body weight by 1 kilogram. Evidence of increased electrolyte retention, and presumably water storage, was found among the latter group. This bizarre situation requires further study with more precise means of measuring energy expenditure. It suggests, however, that striking deviations from accepted metabolic relationships may accompany the spread of cancer.

Whether or not an increased expenditure of energy characterizes progressive growth of cancer in general cannot be decided at present. Significant elevation of basal metabolic rate has been found in some proportion of cancerous individuals by all of those who have investigated the subject. Heindl & Trauner (35) believed that the basal metabolic rate could be correlated roughly with the approximate clinical degree of malignancy of cancer. They thought that a normal rate indicated that a given cancerous lesion was operable. Excision of a neoplasm was followed by decrease in metabolic rate among patients whose metabolism has been increased, and recurrence or metastasis was followed by a rise in basal energy expenditure. Strieck & Mullholland (36) agreed in general with the conclusions drawn by Heindl & Trauner (35) and added the interesting observation that ingestion of egg white by three of their cancerous subjects did not increase the basal metabolic rate. This suggests that the usual specific dynamic action of protein may be masked during certain stages of tumor growth when the organism is constantly rearranging molecules to provide for its needs. The idea is intriguing.

More intensive study of energy expenditure of cancerous subjects is desirable. Controlled clinical experiments have established that diminution in food intake by healthy adults is accompanied by decline in basal metabolic rate (37, 38). What effect does cancer have on this process?

Willis (39) has pointed out that failure of appetite accompanies loss of weight by cancerous subjects. If anorectic cancer patients can not reduce their energy expenditure effectively one would expect them to lose weight more rapidly than would average healthy adults ingesting similar diets. It seems improbable that an increase in total metabolism accompanies the inception of neoplastic growth. Many cancerous individuals preserve their nutritional status for long periods of time even though their lesions are so advanced as to preclude any hope of cure. Perhaps reduction in dietary intake restricts the pathways of intermediary metabolism available to the cancerous host through production of a relative or quantitative deficiency in one or more metabolites particularly sensitive to cancerous growth. No data are available to decide these matters but further investigation is desirable.

The dramatic effects of castration and estrogen therapy on the course of clinical carcinoma of the prostate have increased the span of comfortable, useful life among its victims and reduced the terminal agonal period importantly. The mechanisms by which these procedures produce their beneficial

loss than does free feeding or pair feeding, but the relative quantity of tumor that can be grown without producing undesirable side reactions is smaller. One might interpret the data to indicate that the first phase of tumor growth is prolonged by maintaining a high level of food intake. This is true only in relation to weight loss. Changes in the weights of certain organs that accompany growth of the Walker tumor in rats eating *ad libitum* occur with exaggerated magnitude in tube-fed subjects. Anemia, depression of hepatic catalase activity, and certain changes in the adrenal glands are not prevented (23). This brief summary of studies on the tumor-host relationship considers the reaction of approximately 80 per cent of the subjects studied. The other 20 per cent represented widely variable responses even more interesting than the common one described. Tube feeding did not reduce variation appreciably. The experiments on rats provide a rational basis for clinical investigation in the sense that the basic principles established from the study of this one tumor may conceivably apply to some forms of cancer in man

It is commonly assumed that the average patient with disseminated cancer excretes more nitrogen than he ingests. Such a concept is too general Muller (29), among the first to become interested in the nitrogen metabolism of cancerous subjects, recognized that two of the four cancer patients whom he studied excreted no more nitrogen than did those with non-neoplastic diseases under comparable circumstances The other individuals with advanced cancer did excrete appreciably more nitrogen. Careful scrutiny of his protocols suggests that the latter group contained patients whose cancers were complicated by secondary lesions which of themselves might have been expected to influence nitrogen metabolism Wallersteiner (30) concluded from the study of 12 patients with malignant neoplasms that protein loss occurred only when the dietary intake of nitrogenous substances was inadequate. More recent studies by Homburger & Young (31), Bateman (32), and Waterhouse, Fenninger & Keutmann (33) indicate that patients with extensive cancer commonly retain nitrogen when the dietary intake is adequate. The average healthy adult, however, is usually in nitrogen equilibrium under similar circumstances.

The quantitative adequacy of a diet is determined largely by the energy expenditure of the individual. It is usually considered that maintenance of body weight, or establishment of nitrogen equilibrium or retention, is good evidence of the caloric adequacy of food intake Waterhouse, Fenninger & Keutmann (33) calculated the energy expenditure, by Newburgh's method (34), of eight patients with widely disseminated but different neoplastic or related diseases who ate diets that should have provided enough calorigenic and nitrogenous substances for maintenance of weight in normal persons or subjects not seriously ill with certain chronic diseases. Some of these people stored nitrogen despite a calculated caloric deficit. Waterhouse and her coworkers (33), also found no constant ratio between the amount of nitrogen stored by a cancerous subject and the amount of weight gained Bateman (32) emphasized this point earlier. Some individuals stored nitrogen while

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effects are poorly understood, but they seldom result in complete regression of the cancers. Perhaps a better knowledge of the nutritional requirements of the cancerous host may afford some means of effecting better palliation of cancer patients. It is also probable that cachexia influences the reaction of individuals to those chemicals that are being developed as cancerocidal or cancerostatic agents. Finally, one may hope that a better understanding of the metabolic processes affected by the growth of malignant neoplasms will afford a rational basis for development of more effective anticancer drugs Intensive study of those factors which influence appetite in healthy and diseased individuals is sorely needed.

DISEASES OF THE FEMALE REPRODUCTIVE SYSTEM[1]

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The gynecological literature of the one-year period ending July 1952, presents the usual enormous number of articles which deal mostly with ever-present clinical problems such as carcinoma of the pelvic organs, operative procedures, abdominal pain, menstrual disorders, and infertility. There are no discernible epoch-making advances, but a number of new answers are proferred for old unsolved questions A trend is noticeable in a comparative absence of articles on endocrine problems and the antibiotics in American and English journals, although they are still conspicuous in writings from continental Europe.

GYNECOLOGY

Cancer.—Carcinoma of the uterus remains the major gynecological [illegible]

formations The fundamental question is still "is it cancer?" or is it not The introduction of high-sounding new names such as "carcinoma in situ," "noninvasive carcinoma," "intraepithelial cancer," has not solved anything, and their only contribution has been to intensify histopathological investigations If certain changes occurring in cervical epithelium resemble carcinoma but are benign, do not invade, and are reversible, then they are not carcinoma at all according to our concepts of this disease. Likewise, it is not difficult to conceive that true cancer must start somewhere and hence may be found before invasion into surrounding tissues has taken place. A number of interesting studies have appeared during the past year (1 to 6). Wespi (1) considers preinvasive carcinoma as a special kind of disease which mostly occurs in women under 50 and is connected with sexual function. Westwerdt (2) adds the term "microcarcinoma" to the confusion. Galvin and his co-workers (4) advance further evidence that "carcinoma in situ" eventually becomes invasive, and base their conclusions on biopsy specimens which they feel were originally interpreted incorrectly Some successful attempts are made to diagnose these lesions by vaginal smears [Frerichs *et al* (5)] Moricard (6) thinks that their value is overestimated but that the glycogen content of squamous epithelium may be helpful to eliminate the presence of an intraepithelial carcinoma

As usual there are many reports on the results obtained in the treatment of carcinoma of the fundus, and a general improvement is noted over those obtained previously in five-year periods Most American authorities still

[1] The survey of literature for this chapter was completed in July, 1952.

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(16)]. The subject remained more or less dormant for many years after he pointed out that most of the organs removed in the operating room showed no histologic evidence of disease, but Doyle (17) once more has forcefully directed attention to this practice as still prevailing. Doyle found that 704 normal ovaries were excised during the course of 546 gynecological operations, and it is important to note that in this series he excluded ovaries that were definitely pathological or were from women with carcinoma of the uterus or pelvic inflammatory disease. One of the most probable causes for this surgical furor is the operators' lack of proper knowledge of ovarian pathology, and it may be suggestive that in Doyle's series most of the operations were performed by general surgeons and general practitioners Another possible explanation is found in the report by Patton (18), that in 80 per cent of a group of women operated upon for chronic appendicitis, the cause of the right lower quadrant pain was to be found not in the appendix but in "painful tender ovaries." In justification to this author it must be emphasized that he does not recommend oophorectomy but instead advises the administration of diethylstilbestrol or other "higher dosage estrogen" for this condition. Nevertheless his contention does tend to point to the gonad as the seat of painful disturbances in the absence of demonstrable anatomical disorders and hence tempt interference.[3]

The possibility of a carcinoma arising in an ovary which has been preserved during the course of a hysterectomy performed for a nonrelated lesion is still a subject of debate Thorp (19) observed 10 instances of ovarian malignancy out of 276 pelvic tumors arising after a previous hysterectomy, but Hall (20) states that this complication is rare A plea for conservation of normal ovarian tissue is made by Randall & Hall (21) whenever a one-sided benign growth is encountered It appears that most gynecologists approach this problem in an evasive manner and rest on the patient's age as the criterion, some removing normal ovaries during a hysterectomy whenever the patient is over 40, others over 45, and still others over 50 years old. The illogical solution reached by many is illustrated by Mengert (22) who deplores the vast numbers of normal ovaries removed, and then directs attention to the excessive consideration shown by some surgeons when confronted with a malignant ovarian neoplasm. He observed, in a 10 year period in one locality, that out of 294 women with histologically proven ovarian malignancies only seven received bilateral salpingo-oophorectomy and total hysterectomy The sad results of the treatment of cancer of the ovary in this country is shown by Randall & Hall (23) and in Germany by

[3] An interesting anecdote told to me by Professor Robert Schroeder many years ago may be interposed at this point as also of historical interest. In the early 1910's Professor Salwey at the Rostock Clinic, Germany, believed in "painful ovaries" and as a result his laboratory accumulated many uteri with accompanying ovaries from the operating room Schroeder had the vision to appreciate the value of these specimens and conducted his extensive investigations which led to our understanding of the relationship of the ovarian to the endometrial cycle.

favor preoperative irradiation with radium, e.g., Stearns (7), Scheffey (8), and Payne (9). This procedure has not found favor in Europe, and now McKelvey (10) in this country has expressed the belief that actually it presents no advantage over operation alone when the disease has not progressed to a hopeless degree.

Some startling conclusions based on extensive statistical analyses of cancer of the breast, and applied broadly to other metastasizing carcinomas, are given by McKinnon (11). He criticizes our failure to control these diseases by case-finding programs, and believes that of far greater importance than urging early treatment is to concentrate on determining the "differences in lethal type" of various cancers Schjott-Rivers (12) notes some improvement in the number of survivals from "prophylactic hysterectomy" after irradiation of early cancers of the cervix, but acknowledges that he has insufficient material for final conclusions. Cromer *et al.* (13) describe experiences with palliative treatment of cancer of the cervix and vagina with nitrogen mustard Hohlweg and associates (14) report the healing of a case of chorioepithelioma of the uterus after the administration of estrogen, but their observations are mostly based on the diminution of chorionic hormone exceretion in the urine Morton (15) advances evidence that x-ray irradiation may destroy cancer in regional pelvic lymph nodes, a point well-deserving of further clarification

One of the basic requirements in the training of a gynecologist is a knowledge of histopathology, and it is only natural that studies along these lines should appear regularly each year. The ovary, with its endless numbers of obscure tumors, is always a great hunting ground and the source of bizarre and rare neoplasms Marchetti & Lewis (33) discuss certain homologous ovarian and testicular tumors, and Siebke (34) suggests a classification for ovarian blastomata Stowe & Watt (35) present the second instance on record of an ovarian osteogenic sarcoma and consider the possibility of its origin from a teratoma Lash & Lash (36) discuss stromal myosis, or stromal endometriosis, and its potentialities for malignancy. Piringer-Kuchinka & Turnheim (37) describe two cases of neurofibromatosis uteri accompanying von Recklinghausen's disease, and Stange (38) reports a new growth which he believes is the first case of a "glomus tumor" of the clitoris.

Ovariectomy—The father of abdominal surgery, Ephraim McDowell, paved the way by successfully performing an oophorectomy for a large cyst, but little did he reck that in time a frightful sacrifice of normal ovaries would ensue A peak in the rate of this deliberate gonadal slaughter was reached toward the end of the nineteenth century, and the procedure was defended by many gynecologists in numerous acrimonious debates One of its ardent advocates was Dr. Battey of Georgia, and a wit referred to the operation as "batteyizing" a patient. A formal discussion of this question was held before the American Gynecological Society in 1893, and probably few realize that one of the first truly authoritative voices raised against the wholesale removal of normal ovaries was that of J. Whittridge Williams [Tyrone

well illustrated by the continued profusion of papers on operative procedures It has been estimated, for instance, that during the past 15 years 600 articles and references dealing with urinary and genital fistulas have appeared in the *Zentralblatt für Gynaekologie* alone [Budniok & Muller-Meernach (39)]. At the moment, interest is centered on stress incontinence and the Marchetti operation which depends on a suprapubic approach for a suspension of the urethra and is considered superior to the older types of sling operations [Chalmers (40)].

Abortion—Any safe and sane medical approach to the induction of an abortion for therapeutic indications would be welcome in order to avoid or diminish the hazards of surgical intervention. However, some methods at present under investigation in Germany are scarcely to be accepted with much enthusiasm in this country. The "method of Boero" consists of injecting a solution of formalin into the gestation sac. It is usually done through the cervix, but Jürgens (46) prefers to inject directly through the abdominal wall when the period of gestation is between four and six months. Out of 206 cases, Nölle (47) had no deaths, and although the abortion occurred within seven days in 64 patients, there was a delay of from one to four months in five instances. Neideck (48) considers the method interesting and revolutionary, and believes that it only remains to determine if there results any injury to the mother's internal organs. Manstein (49) employs a solution of sulfapyridine instead of formalin, and Kallenback (50) injects a 25 per cent solution of glucose extraovularly by passing a small catheter between the uterine wall and the gestation sac. Approaching the problem in a simpler and saner manner, Thiersch (51) found that abortion resulted in 10 out of 12 women after the oral administration of the anti-folic substance aminopterin (4-aminopteroylglutamic acid)

Pain—The patient with abdominopelvic pain with an absence of palpable lesions of the female pelvic organs is still one of our basic gynecological problems and seemingly receives relatively little attention It is of vital importance from many standpoints, and is responsible to a great extent for many needless operations Theobald (52) states that this condition and its associated manifestations was "perhaps more fully recognized in England a century ago than it is today." It is characterized by pain and burning sensations in one or the other lower quadrant of the abdomen with or without radiation down the thigh, backache, pain on defecation, pruritus, dyspareunia, dysmenorrhea, and various menstrual disorders The obscurity attached to the etiology of this syndrome is well demonstrated by the numerous names which have been given to it—pelvic sympathetic syndrome, plexalgia hypogastrica, broad ligament neuritis, spasmophilia genitalis, chronic parametritis, spastic parametropathia, pelvic congestion, and parametritis posterior chronica. The variable manifestations of the disease, the lack of recognition of a simple, well-defined clinical entity or common etiological factor, and the multiplicity of therapeutic agents advocated, are only equalled by the enthusiastic fervor with which investigators of the past

Schroeder & Hartl (24). An effort to develop a newer method of therapy is reported by Anderman *et al.* (25) in employing nitrogen mustard for dysgerminoma ovarii.

Infection.—The first description of pyometra is ascribed to John Clarke of London in 1812, and since that time it has been the subject of discussion at sporadic intervals. Two outstanding contributions have appeared during the past year. Henriksen (26) has analyzed 118 cases where the pyometra resulted from benign lesions leading to occlusion of the cervix uteri. The three common causes were found to be cicatrization of the cervix following the use of the electrocautery, cervical occlusion in the post-menopausal age, and complications of pregnancy, especially subsequent to criminal interference. The seriousness of this disease is amply demonstrated by the incidence of 20 deaths in this series. The second report includes an extensive bacteriological study and records that in almost 75 per cent of cases it is a complication of malignancy of the cervix or fundus, and most often after irradiation [Carter *et al.* (27)]. Neither report presents instances occurring following endocrine therapy, but two French authors describe a case of hematocolpos which suggests this possibility [Melchior & Camey (28)]. Their patient was a woman of 69 who had a stricture of the vagina and had been treated for four months with estrogens and androgens, leading to functional uterine bleeding.

The incidence of trichomonas vaginitis is discussed by Whittington (41), and treatment with topical applications of aureomycin is recommended by Greenblatt & Barfield (42). The subsequent appearance of moniliasis in 8 per cent of cases, however, will not appeal to most gynecologists. The diagnosis of tuberculous endometritis by culture of uterine secretions seems a step forward [Halbrecht (43), Kirchhoff *et al.* (44)]. A syndrome consisting of various functional urinary symptoms such as accompany hypertrophy of the prostate in men is described by Tholen (45). He only presents one case but he says that it is frequent, and with gallic candor he discusses so-called "prostatism" in women!

Phlebitis.—A number of articles on the ever-present threat of phlebitis with dreaded pulmonary emboli have appeared in American, English, German, and French literature without advancing our knowledge of the subject to any remarkable degree. Enjalbert (29) and Pollosson *et al.* (30) discuss treatment, and especially the employment of anti-coagulants. The figures of Koller (31) giving the incidence of thrombosis and emboli in his clinic in Basle, Switzerland, are of interest During the period 1922 to 1941 there were 1.4 per cent of cases in obstetrics and 12 per cent in gynecology, with mortality rates of 0.2 per cent and 2 2 per cent respectively. Since in some instances of suppurative thrombophlebitis it becomes essential to ligate the inferior vena cava, the assurance that this grave procedure does not interfere with subsequent ovarian function and pregnancy is encouraging [Collins *et al.* (32)].

Plastic surgery.—The importance of plastic operations in gynecology is

nitrate stick, and at times also of an injection of procaine into the abdominal wall along the rectus muscles His results are truly astounding. He obtained a "cure rate" varying from 87 to 100 per cent for lower abdominal pain, backache, dyspareunia (deep penetration), stress incontinence of urine, and "all disturbances of micturition" in a large series of patients.

MENSTRUAL CYCLE

The "menstrual wave" theory, enunciated by Goodman in 1875, supported in a classic thesis by Mary Putnam Jacobi in 1877, and further propounded by Stephenson in 1882, seldom receives recognition in modern writings This is rather unfortunate because many of the claims it made for periodic metabolic changes accompanying the menstrual cycle are constantly being substantiated The best-known example is the basal body temperature curve, which is widely employed for the determination of ovulation time in clinical studies It is refreshing, therefore, to find references to both Goodman and Jacobi by two independent groups of German investigators. Wachholder & Dahn (58) note a premenstrual rise of arterial pressure and an increase in both red and white blood cells during the premenstruum, but strangely enough they saw this change only in women with dysmenorrhea, and they claim that in "normal" women there may even be a reversal of these findings Doring & Schaefers (59) made a thorough study of variations of the size of the pupil, controlling the stages of the cycle by basal body temperature observations. They found that the pupil is smaller during the premenstruum as compared to the postmenstruum Since this transformation is apparent two days before the rise in body temperature they consider it a sign of ovulation. Doring & Weber (60) also found a decrease in serum protein of 0.5 to one per cent both shortly before the onset of menstruation and for one day at a time corresponding to the ovulatory rise of temperature.

Enzymatic relationships.—The extensive investigations of the past two decades have provided us with a working knowledge of the endocrine control of the menstrual cycle and this type of research has more or less reached a dead end. This impasse, however, has not discouraged further quests for closer understanding and two lines of approach appear on the scene to broaden our concepts of hormonal activity. The first is the study of the interrelationship between hormones and enzymes and other chemical entities A number of studies, mostly in corroboration of previous work, have appeared during the year under consideration. For example, Fishman *et al* (61) noted low values of β-glucuronidase in the vaginal fluid at the time of ovulation, coincident with the high peak of estrogen production, and also after the administration of diethylstilbestrol Augustin (62) believes that the presence of glycogen in the epithelial elements of the endometrium begins with the formation of a mature follicle and continues throughout the postovulatory phase The nucleic acid content of the endometrium, on the other hand, is high during the estrogenic phase and recedes after ovulation [Vokaer (63); Bremer *et al.* (64)] In an extensive study of the enzymatic activity of the

have approached the question from one or another biased viewpoint. At first held to be a question of neuralgia, an "irritable uterus," the disease became associated with inflammatory lesions of the cervix, parametritis with involvement of the utero-sacral ligaments, pelvic circulatory changes, and disturbances of the autonomic nervous system.

Recent contributions do not forecast any early solution, but indicate that attention is directed chiefly to involvement of the nervous system and also implicates psychosomatic medicine. In a review dealing with the physiology of pain Gerard (53), although not dealing specifically with the gynecological aspects of the disease, points to "burning pain" as a characteristic of causalgia, and states that this disorder may be regarded not "as a result of overdriving but of loss of impulses, as defective rather than excessive innervation." Somewhat similar explanations are given by Skajaa (54), Theobald (52), and Eller (55). Skajaa (54) presents detailed diagrams illustrating areas of hyperalgesic zones in the skin of the abdomen which point to the segment of the spinal column involved He also believes that the pain-relieving effect of resection of the presacral nerve is not from severance of the pain-conducting tract, but from a severance of the efferent fibres which convey impulses from the autonomic nervous system to the uterus. It thus indirectly produces a cessation of the abnormal flow of impulses to the medulla. In an extensive discussion Theobald (52) suggests that

> the threshold of pain of one or more nerves to the uterus and/or the parametric tissue may be lowered for months or even years . . the simplest working hypothesis, though it may not be correct, to explain the fact that over-stimulation of nerves deriving from T 12 and L 1 can cure pain in areas supplied by S2, 3, 4, is to assume that there is a block representation for pelvic pain in the cerebral cortex.

Eller (55) directs attention to abdominopelvic pain which is of somatic, not visceral, origin and considers that the cause in many instances may be found in irritative lesions of the spinal nerves The association of abnormal mental disturbances in these patients was advanced by Hirsheimer (56) among others, who found that "tension states" were present in 42 per cent of a group of women with subjective pain, but in only 27 per cent in another series with no complaints referred to objective findings. Duncan & Taylor (57) emphasize the importance of emotional disorders which in time lead to pelvic congestion and a long train of symptoms. They found that

> psychiatric study of 36 patients with pelvic congestion revealed that they had experienced in childhood almost no secure family life after which to pattern their own subsequent existence. . . . Inability to function adequately as a woman, either sexually or maternally, was displayed by most

In keeping with his thesis as to etiology, Eller (55) obtained satisfactory improvement in his patients by paravertebral nerve-root block, using a solution of procaine and Dolamin (a proprietary containing benzyl alcohol, ammonium sulfate, sodium chloride and water). Theobald's (52) usual method of treatment consists of cauterization of the uterus with a silver

Taubenhaus & Soskin (77). Other parasympathetic stimulants have been employed in animal experiments, and it is mantained that they may disturb the estrous cycle of adult mice and re-establish genital function in senile animals (74, 75, 76) The same authors claim that it is impossible by such means to bring about gonadal activity in immature animals, although Fluhmann (78) found that the preliminary administration of neostigmine enhanced the increase of ovarian weight induced by the chorionic hormone in young rats. It also has been possible to effect a precocious opening of the vaginas of immature rats by the daily injection of neostigmine [Fluhmann (79)].

Sex determination—The prenatal determination of the sex of a baby always has had a particular fascination for all peoples. It has been a great boon to quacks and faddists who have fared well since at the best they have a fifty-fifty chance of guessing correctly In olden times the expert merely waved mystic wands or glared soulfully at the expectant mother's urine, but during the past 25 years the advances in our knowledge of the endocrine factors concerned with pregnancy have led even serious students to delve into this mystery. The past year has seen additional reports but no claims of one hundred per cent accuracy. Rosa & Fanard (80) base their predictions on the cytology of the liquor amnii and Langreder (81) on the cytology of vaginal fluid, while Finke (82) studied a skin sensitivity reaction from the intracutaneous injection of testosterone propionate Rapp & Richardson (83) applied the Richardson test to saliva obtained from women pregnant six months or more. In nearly every case the positive tests were associated with a male, and most of the negative with a female child The Richardson test is usually performed with urine or serum. It is a chemical procedure for the identification of free estrogen, and an accuracy is claimed of 99.1 per cent for the diagnosis of pregnancy (84). Furthermore, for ten dollars a commercial concern offers an "outfit" complete "with reagents, glassware, and copyrighted instructions" to the medical profession (85)!

Bleeding—The treatment of functional bleeding with various sex hormones is still recommended [Greenblatt & Barfield (89, 90)], but one would scarcely accept the widespread usage of testosterone as a routine treatment of fibromyomata uteri advocated by Aimes (91). Allen *et al.* (92) present evidence that in certain hemorrhagic metropathias, an inhibitor to blood clotting is present. The nature of this inhibitor is not determined but it can be measured by a quantitative method of titration described by the authors. It also can be neutralized by protamine sulphate and toluidine blue, so that the administration of these substances may offer a therapeutic approach to the control of certain cases of abnormal uterine hemorrhage Of 62 patients with uterine bleeding 47 (75 per cent) had an elevation in protamine titration Half of these were given toluidine blue or protamine sulphate while the remainder were followed as controls and received other treatment or none All but four of the experimental cases reported improvement and the majority experienced complete relief for varying periods of time. A promising advance in the therapeutic field of uterine bleeding, especially in cases of

human endometrium, Stuermer & Stein (65) reach the conclusion that highest values for aerobic glycolysis occurs during the secretory stage, an effect opposite to that in anaerobic glycolysis. However, the activities of malic and succinic dehydrogenases, cytochrome oxidase, and adenosine triphosphatase rise during the proliferative phase and attain their maximal activity early during the stage of secretion.

Autonomic relationship.—The second approach is concerned with the influence of the autonomic nervous system on the genital cycle, and mostly involves pharmalogical methods. The subject is still confused, but received a great stimulus from the development of the so-called "neostigmine presumptive test for pregnancy" introduced in 1940 by Soskin, Wachtel & Hechter (66). It consists of giving a patient, whose menses are overdue, three consecutive daily subcutaneous injections of 1 cc. of a 1:2000 solution of neostigmine (Prostigmine). If she is not pregnant, uterine bleeding ensues within 24 hr. after any one of the three injections, but in the presence of a gestation there is no flow. The accuracy of this procedure has been attested to by many observers, although the patients must be selected and not include those of the menopausal age nor of clear-cut "endocrine disorders." An analysis of many reports from the world literature, based on 1055 cases, showed 91.3 per cent correct, and 8.7 per cent incorrect diagnoses, or 97.2 per cent correct in pregnancy and 86.1 per cent in functional amenorrhea [Elert (67)]. These figures are generally lower than those reported in American journals. Some instances of "delayed reactions," especially in amenorrhea of long standing where bleeding does not set in for a good many days (68), cause one to wonder if they should be considered as anything but negative responses. The employment of acetylcholine by Geisendorf (69) will be questioned by pharmacologists who appreciate the difficulties associated with the administration to humans of this toxic substance in a pure fresh form. Glatthaar & Aeppli (70) warn that not only neostigmine but benzazoline (2-benzyl-2-imidazoline hydrochloride; Priscoline) may act as abortifacients, but the number of proven cases they offer in evidence is not impressive. These studies inevitably have led to the recommendation that neostigmine be employed along with estrogen and progesterone in the treatment of functional amenorrhea [Gitsch (71, 72)] but judgment on this procedure should be reserved for the present.

The original employment of neostigmine in the manner discussed above was based on the work of Reynolds (73), who found an increase of the acetylcholine content of the uteri of spayed rabbits given estrogen. It was thought that this accounted for the uterine hyperemia associated with estrus and hence might be concerned with menstrual bleeding. Neostigmine produces an acetylcholine effect by inhibiting its destruction by the enzyme cholinesterase, and therefore its effect in the so-called pregnancy test has been interpreted as a result of a direct parasympathetic stimulation of the uterus However, the possibility of an endocrine stimulation involving the hypothalamus and the anterior hypophysis is supported many observers [Gitsch & Tulzer (74); Nordmeyer (75); Willig (76)], and was originally advanced by

(99) found that follicular ova of the rat could be transferred to the ovarian bursa of mated recipients, fertilized, and grow to become normal animals, genetically the product of their parents Umbaugh (100) was concerned with superovulation and ovum transfer in cattle. On the basis of observations in the rat Blandau & Odor (101) have offered much information on the sperm penetration of ova. Further data on this score has been presented by Moricard & Bossu (102), while Lagerlöf (103) has discussed hereditary forms of sterility in cattle breeds The international aspect of these investigations is interesting since the authors were from France, Sweden, and the United States, and the papers were presented in this country.

At one time, infertile patients were almost altogether in the hands of the gynecologist, the male was completely ignored, and treatment consisted of correcting real or imaginary defects of the female pelvic organs. We like to think that unnecessary suspensions of the uterus, curettages, and plastic repairs of the cervix are a thing of the past, but an analysis of operations performed on 500 infertile wives indicate that this approach is still much abused [Carter *et al.* (104)]. These writers found that

various pelvic operations (major cervical, suspension, tubal and ovarian procedures) are associated with a reduced incidence of pregnancy These operations are done usually without adequate study of the couple. Gynecologic abnormalities (excluding chronic adnexitis) for which these procedures are performed are not a major cause of infertility. A much more critical attitude toward operation on sterile wives is greatly needed.

The enthusiasts who advocate small dosage x-irradiation of the pituitary area and the ovaries for menstrual disorders are still in evidence Asherman (105) found that combining these two methods of irradiation gave twice as many good results and the most encouraging results were in cases of menstrual disorders without organic changes. He reports success in establishing a pregnancy in from 23 to 34 per cent of cases. A warning is found, however, in his statement that a premature menopause occurred in 50 per cent of his patients who received this treatment after the age of 35.

The fundamental studies of Rubin with utero-tubal insufflation have given a great impetus to investigators of sterility and his procedure is an absolute essential in clinical work. Decker (106), continuing his outstanding work with the culposcope, has found that manipulation using this instrument at the time of a utero-tubal insufflation enables the release of occluded tubes which otherwise would require laparotomy Pollock & Preiskel (107) recommended a water-soluble, instead of oily, medium for hysterosalpingography Tubal plastic operations still occupy much thought, and various procedures are attempted to improve on the bad results of the past Hellman (108), for instance, uses polyethylene tubing to "splint" the fallopian tubes after repair of the occlusion Israel (109) reports that the incision of fallopian tubes along the superior surface, from the fimbriae to the uterine cornu, is a favorable approach to obtain functional organs in the presence of acute suppurative inflammation. He strongly advocates nonoperative treatment of acute salpingitis, however, and emphasizes that this operation should only

emergency, is the intravenous administration of a suitable preparation of estrogen [Greenblatt & Barfield (93)]. An increased excretion of gonadotropins following the administration of ACTH and cortisone may prove a valuable step in our understanding of the intricate interrelationship of adrenal and ovary [Sohval & Soffer (94)] The investigator with ethereal flights of fancy is still with us, as shown by the report of Botella-Llusia (95). According to this author the adrenal contains a potential third gonad in a juxtamedullary location deep in the cortex which, however, only develops in the absence of normal gonadal secretion No doubt he has in mind the "zone X" of the mouse adrenal, but its existence has not been demonstrated in the human. Nevertheless, he considers it worthy of a number of recommendations for clinical application.

Miscellaneous.—An interesting, although rare, clinical entity, which they call a "hyperhormonotrophic syndrome" and characterized by excessive uterine bleeding, galactorrhea, and hyperthyroidism, has been described by Zondek *et al* (86) The removal of an adrenal cortex tumor in a 28-year-old woman who had never menstruated, resulted not only in an appearance of the menses but in a normal pregnancy [de Paiva *et al* (87)]. A coincidental observation is that the abnormal hair present on her thorax and limbs disappeared, but the apical baldness, which so often accompanies hirsutism, remained. Oehler (88) conducted an anatomical study of the ovaries of fetuses and infants and could neither confirm the origin of oogonia from germinal epithelium nor a massive degeneration of primary follicles at the time of birth Since other observers long ago postulated the origin of oocytes from cell rests in the hilus of the ovary, this finding does not refute the modern concept that ova are newly formed throughout the whole reproductive life of an individual

INFERTILITY

Always of great interest to the gynecologist, problems associated with infertility have been subjected to intense investigation in the past few years. The urologist and veterinarian have contributed their services, special societies have been established in many countries (for example, the U S. A., England, Mexico, Brazil), an international organization is on the way, journals solely devoted to the subject have been founded, and a number of physicians now limit their efforts to the practice of this specialty The American journal *Fertility and Sterility* is now in its third year and is notable for the high caliber of its contents A set of "minimal requirements" deemed necessary for the proper clinical investigation of infertile couples has been prepared by the American Society for the Study of Sterility and has become the basis for introducing the subject at medical assemblies [Mengert (96); Overstreet (97)].

Many of the contributions to the study of infertility are based on fundamental animal experimentation, a feature which presages well for the future. For instance, Chang (98) conducted an extensive study of fertility and sterility, as revealed in the fertilization and development of rabbit eggs. Noyes

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be employed when the abdomen has been opened and *this condition found* as the result of a diagnostic error. This quaint recommendation is indeed startling. If linear salpingostomy is an effective method of treatment why should it not be widely employed? Conversely, if the treatment of choice in acute salpingitis lies in the employment of antibiotics, why should a reservation be made for the individual whose abdomen is opened inadvertently? It long has been common practice among conservative gynecologists merely to acknowledge the mistake, close the abdomen without resorting to meddlesome manipulation, and then continue with medical therapy.

A number of reports direct attention to the incidence of uterine malformations as important factors concerned with infertility, and particularly in instances of habitual abortion [Halbrecht (110); Fenton & Singh (111); Steinberg (112)]. This field has probably been neglected and deserves further consideration. Bergman & Lund (113) note that the osmotic pressure of cervical mucus undergoes cyclic changes. At ovulation it is isotonic with normal saline, as with human semen, and becomes higher at other times. The character of the cervical secretion (fern-like pattern; "spinnbarkeit") at the time of ovulation or following estrogen therapy has been emphasized, and the possibility of employing this finding in clinical studies is discussed by Roland (114) and Cohen *et al.* (115).

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VASCULAR DISEASES OF THE BRAIN[1]

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The subject of vascular disease of the brain is never far from us. Of all the forms of neurological disorder it undoubtedly ranks first in frequency and gravity For this reason the reviewers believe it altogether fitting and proper that the neurological section of *Annual Review of Medicine* for 1952 should be devoted to a critical analysis of recent scientific work in this field.

Interest in the subject of vascular disease of the brain is not new, in fact since the very beginning of the modern era of scientific medicine our profession has been cognizant of its importance However, in the past few years, stimulated by the rising incidence of vascular disease in our aging population, the cause and pathogenesis of these conditions have been investigated with increasing vigor As a result, a prodigious number of articles have been published. The reader may gain some notion of the immense literature in this field by referring to the annotated bibliography on the physiology of the circulation from 1938 to 1948 by Kenk & Nall (99) which contains more than 4000 titles.

To summarize all recent publications on this subject is a task far beyond our limited means. The plan which we propose to follow is to present only the practical aspects of vascular disease which have received some clarification in recent years. Wherever possible, new scientific data are interpreted and criticized in the light of our own personal experience with these diseases in the clinic and the pathological laboratory.

Classification of Vascular Diseases of the Brain

The period of 1850 to 1950, when reviewed in historical perspective, may be regarded as the morbid anatomical period of vascular disease It is during this time that many of the principal clinico-pathological syndromes were delineated. Three major types of vascular disease have emerged, these are the metabolic or degenerative, the developmental, and the inflammatory.

The metabolic and degenerative lesions of blood vessels are usually designated by the term arteriosclerosis Included in this group are atherosclerosis, hyaline arteriosclerosis, hyperplastic, and necrotizing arteriosclerosis Monckeberg's arteriosclerosis, a condition in which the media of the vessel

[1] The survey of literature pertaining to this review was completed in September, 1952.

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bitis associated with all types of meningitis and from the thrombophlebitis incident to infections of the ears, paranasal sinuses, and blood stream. The inflammatory diseases of brain arteries often affect the brain by obstructing its blood supply in one or more places. Less often there is a rupture of vessels and hemorrhage into the brain substance or the meninges. In polyarteritis nodosa, through the intermediary of renal disease, hypertension, lupus erythematosis and scleroderma a hypertensive encephalopathy may be induced.

The classification of vascular disease of the brain commonly employed in both the clinic and the pathology laboratory is based on the underlying pathological process, if known In the case of encephalomalacia, the presumed cause of the infarction, whether arterial thrombosis or embolism or venous thrombosis, is stated, and sometimes it is possible to specify the cause of the vascular lesion as well. In hemorrhage, where it is often impossible to be explicit concerning cause and pathogenesis, the process is designated solely by its effect on the brain, *viz.* hemorrhage.

Classification requires exact knowledge of the attributes of a disease entity. Recognition of the differences between these various and sundry forms of vascular disease of the brain represents the major achievement in this field in the past century Obviously many details, which can be learned only by more thorough morphological studies and by the employment of new and more refined histological techniques, remain to be described. The delimitation of pathological processes is acknolwedged to be one of the first steps in the progress of scientific medicine.

Incidence of the Different Types of Vascular Disease of the Brain

Surprisingly little factual information concerning the frequency of the different types of vascular disease of the brain is available There are probably several reasons for this hiatus in our knowledge Until recent years pathological diagnosis was inexact, and even now there is still a difference of opinion amongst pathologists as to the criteria for diagnosis Obviously, if one pathologist calls a hemorrhagic softening an infarct and another labels it a hemorrhage then their statistics on the same type of pathological material will be at variance. Furthermore, in very few hospitals or clinics is the pathological material sufficiently large and unselected to permit a meaningful survey.

Our own statistics are probably as good as most of those in the literature and certainly more reliable than some In 1947, a survey of the neuropathological material at the Boston City Hospital[1] showed that in a four year period between January 1942 and January 1946 vascular lesions were found in 23 5 per cent of all cases in which the brain was examined [Adams & Cohen

[1] This is a large municipal hospital that accepts all types of patients, mainly from the lower income group.

becomes calcified, has not been observed in brain vessels, although calcification secondary to atherosclerosis may occur in the vertebral and internal carotid arteries. Further distinction has been drawn between the pathological processes that lead to arterial and arteriolar sclerosis. These different types of arteriosclerosis produce several types of change in the brain. Atherosclerotic thrombosis and embolic occlusion of brain arteries cause focal, ischemic necrosis of tissue, a state designated as softening, infarction, or encephalomalacia. Hyaline and hyperplastic arterio- and arteriolosclerosis result in a fraying of the tissue (*état criblé*) around the vessels and in the formation of small foci of ischemic necrosis (*état lacunaire*); but these relationships have not been settled with finality. Hyperplastic arteriosclerosis and necrotizing arteriolosclerosis result in multiple small hemorrhages and ischemic foci which are often associated with brain swelling. This group of pathological findings is called hypertensive encephalopathy or pseudouremia. Massive hemorrhage into the brain or meninges, which occurs as a rule only in patients with severe hypertension, cannot be attributed to any one type of vascular change but is frequently associated with hyaline, hyperplastic, and necrotizing arteriosclerosis and, according to some workers, with dissecting or miliary aneurysms of small arteries.

The second class of vascular diseases, those resulting from a fault in development, comprises the congenital aneurysms and the angiomas or hemangiomas. The latter are not tumors in the strict sense of an actively growing tissue, but consist of an accumulation of blood vessels of abnormal size and type for a given locale. These developmental anomalies characteristically produce hemorrhage into the substance of the brain or in the meninges, but may at times expand and create an increase in intracranial pressure. The vessels within these malformations rarely become thrombosed with resulting infarction of brain tissue. The hemangioblastoma, which is composed of endothelial cells, is often classified with this group but differs in that it forms a cystic tumor, usually in the cerebellum or spinal cord. Also, there is frequent concurrence of pancreatic cysts, angiomas of the liver, and hypernephroma (Lindau's disease) or hemangioma of the retina (von Hippel's disease).

The third class of vascular disease consists of several types of inflammatory lesions of arteries and veins, and is not as well differentiated as the other two. Syphilitic arteritis (Heubner's endarteritis), the best known example, received intensive study during the nineteenth century but must now be regarded as a vanishing disease. *Several other pathological entities have been* discovered in recent years, but it is fair to say that as yet their morphology [illegible] Included in [illegible] ob- [illegible] no- dosa and the arteritis of disseminated lupus erythematosus, and possibly other "rheumatic diseases." In these diseases the affection of blood vessels is the primary change. In this respect they differ from the arteritis and phle-

We have not had a single proven case of Buerger's disease of brain arteries, or of "rheumatic arteritis."

Other statistical analyses of vascular disease of the brain should be brought to the reader's attention. Rupp, Riggs & Statemeyer (145), in a study of 149 cases of apoplexy under 60 years of age, found hemorrhage in 71 and encephalomalacia in 78. Hicks & Black (87), in a review of 155 autopsied cases of vascular disease of the brain, report that 118 were of "hemorrhagic type" However, it is impossible to determine what proportion of these cases had a massive hemorrhage by our classification or hemorrhagic infarction, for the authors do not distinguish between these two pathological entities. They believe that both conditions are based on the same underlying pathological change, an ischemic damage to small vessels, and therefore have grouped them together. Moreover, they did not attempt to distinguish between thrombotic and embolic occlusion. In fact, intra-arterial clots were found in only 12 out of 23 cases of brain infarction They attributed softening to vascular spasm in the other 11 cases.

Massive Brain Hemmorrhage

The main clinical and pathological characteristics of brain hemorrhage were fully described during the nineteenth century. The almost invariable association of arterial hypertension and arteriosclerosis, the frequent concurrence of kidney disease and hypertrophy of the left ventricle of the heart the abrupt onset and rapid progression of the clinical neurological symptoms leading, in most instances, to death in a few hours to days; the common clinical manifestations of deepening coma and hemiplegia; the sanguinous cerebrospinal fluid under increased pressure; the pathological finding of a massive blood clot, usually in the lenticular nucleus, internal capsule and thalamus, and less often in the cerebral white matter, pons or cerebellum,—all these are the commonly recognized attributes of this disease.

The cause and pathogenesis of brain hemorrhage have proved to be elusive, and indeed they remain obscure to this day. The chief obstacle to our study of these problems has been that the pathological process occurs with such violence that it destroys evidence of its own causation. Two basic conditions, arterial hypertension and disease of the blood vessels, are assumed to exist in every case. As long ago as 1855, before arterial blood pressure could be measured at the bedside, Kirkes (102) observed hypertrophy of the left ventricle of the heart in 17 of 22 cases dying of brain hemorrhage This idea is well expressed in the aphorism that "the large heart breaks the weak vessels." Evidence of hypertension can be found in nearly all cases dying of [illegible]

14 per cent [Janeway (94)] of hypertensive patients ultimately die of brain hemorrhage Jackson (93) and other clinicians of the nineteenth century taught that renal disease disposes to hemorrhage and not to softening, which is another way of stressing the importance of hypertension.

(6)]. During this period there were 2670 autopsies and the brain was examined in approximately 1400 (all those in which there was no autopsy restriction[3]). Another survey in the same hospital was made in the year 1949 when there were 179 cases of vascular disease of the brain in 925 autopsies [Fisher & Adams (61)]. Of the latter, the brain was examined in 740 cases, giving an incidence of 19 per cent of total autopsies or 24 per cent of those with examination of the brain (see Table I). Thus in the pathological material of a municipal hospital at least one of every five patients had some form of vascular disease of the brain at the time of death.

TABLE I

INCIDENCE OF VASCULAR DISEASE OF BRAIN PROVEN BY AUTOPSY AT BOSTON CITY HOSPITAL, 1949

Total number of autopsies	925
Total number of brains examined	740
Number of cases of cerebrovascular disease	179 (*24 per cent*)
Brain infarction or encephalomalacia	129
Embolism	57
Atherosclerosis and thrombosis of a large artery	21
Atherosclerosis plus multiple small infarcts	34
Indeterminate	17
Massive hemorrhage	28
Hypertensive encephalopathy	7
Ruptured saccular aneurysms	5
Vascular malformation	3
Tuberculous meningitis and arterial thrombosis	3
Cerebral vein thrombosis	2
Polyarteritis nodosa	1
Vascular syphilis	1

In a report on brain embolism, Fisher and Adams tabulated the relative incidence of the different types of vascular disease of the brain. These data are also presented in Table I.

These figures do not differ significantly from those obtained at the Massachusetts General Hospital, where at least part of the case material is more highly selected In both hospitals the high frequency of embolism is noteworthy. Also, softening of the brain has occurred four to five times as often as hemorrhage, accounting for about 80 per cent of all cases of apoplexy. The incidence of vascular malformations and the different types of inflammatory diseases has been low in our autopsy material In some years only one or two such cases have occurred, whereas in other years there have been several.

out that some of the transitory apoplectic attacks in hypertensive patients must surely be a result of vascular spasm. Further, localized arteriolar constriction can actually be seen in the retina and has been observed in pial arteries during neurosurgical operations. This angiospasm is said to give rise to necrosis of the walls of the blood vessel distal to the point of constriction, and to the brain tissue nourished by this vessel. [The damaged artery ruptures during the period of vasodilatation (or vasoparalysis) which follows the vasoconstriction.] This angiospastic hypothesis is almost impossible to affirm or refute. The experiments of Ricker (141) are often cited in its support, but since they were carried out on the pancreatic and the ear vessels of rabbits, their relevance to the problem of vascular disease of the human brain is dubious, to say the least.

Another intriguing explanation of brain hemorrhage was proposed by Rouchaux (144) and elaborated more recently by Globus & Strauss (76) and Hiller (89). They argue that the artery dilates and ruptures only when an infarct has previously occurred, thus depriving the vessel of its normal support. They point out that one or many infarcts are present in cases of brain hemorrhage, and that the hemorrhage is often found within an older focus of softening. There have been several attempts to test this hypothesis experimentally but typical brain hemorrhages have not been produced. Broman (23, 24) showed that microembolism damages blood vessels and produces brain infarction, but hemorrhage into the softened tissue occurred only after the blood pressure had been raised by injections of adrenalin. Globus and his associates (75) obtained essentially the same results in dogs by first creating an infarct and then giving neosynephrine to elevate the blood pressure.

Observations of our own pathological material do not permit a definitive statement as to the cause and pathogenesis of brain hemorrhage. Routine examination of the vessels in the cerebral hemisphere opposite to a "capsular" brain hemorrhage has so far failed to disclose a uniform type of vascular lesion. We have frequently observed the miliary aneurysm of Charcot and Bouchard in the cerebral cortex or basal ganglia of cases dying of malignant hypertension. However, in our opinion this lesion is merely an organized arteriolar hemorrhage, and the correlation between it and massive brain hemorrhage may be mere coincidence of small and large hemorrhages in states of severe hypertension and arteriosclerosis If this is true, then one must look further for the cause of both the miliary aneurysm and the brain hemorrhage We have been unable to demonstrate brain hemorrhage in anatomical relationship to infarction except in cases of ruptured saccular aneurysm with meningocerebral hemorrhage. Considering the semisolid consistence of the brain tissue it seems improbable that normal tissue could offer more support to a vessel than softened tissue.

There is still need for careful pathological study of the brain vessels in cases of hemorrhage. A regrettable tendency has occurred in recent years to make elaborate deductions as to the functional state of the brain vessels

Very few inquiries concerning the tensile strength of brain arteries have been made. Lampert and Mueller (106) injected the carotid arteries of cadavers, with and without arteriosclerosis, before the skull was opened and found that the brain arteries could withstand pressures as high as 1520 mm. of Hg for 6 min. Also, Glynn (77) injected air in vessels under pressures that were more than two times the highest recorded arterial pressure without rupture of the vessels. Intravascular pressures of this height, so far in excess of those recorded during life, have led some observers to minimize the role of hypertension. However, we are not prepared to accept these observations as final, for during injection studies of arteries, after the brain has been removed from the skull, we have on several occasions ruptured one or more arteries with intravascular pressures of 200 to 250 mm. of mercury.

Attention has been focused on the pathological changes that cause the brain vessels to weaken and eventually rupture. This aspect of the subject was reviewed by Stern (157). During the latter half of the nineteenth century nearly all pathologists were convinced that the aneurysm of Charcot and Bouchard (32) was responsible for massive brain hemorrhage. This aneurysm is a firm, round or oval, white or brownish-colored nodule about 0.5 to 2 0 mm in diameter and is attached to a small artery or arteriole in the cerebral cortex or basal ganglia. Lowenfeld (115) and other pathologists later challenged this theory. They were unable to find these aneurysms in some cases of brain hemorrhage or failed to demonstrate any relationship between such aneurysms and hemorrhage in other cases. Furthermore, after closer study it was concluded [Eppinger (53)] that the miliary aneurysm is, in fact, a false or dissecting aneurysm or, in the terminology of Pic (136) and Ellis (50), an organized adventitial or perivascular hemorrhage. Shennan (152) agreed with the latter interpretation and stated it was inconceivable that a lesion of this type in a small artery or arteriole could give rise to a massive brain hemorrhage.

After the miliary naeurysm was discredited, several alternative hypotheses were put forth Fatty and granular degeneration of the brain vessels was postulated by Lowenfeld (115), and Shennan (152) proposed that arterial disease causes a local weakening and dilatation in the arterial wall which finally ruptures. Acute necrosis of many small brain vessels, a result of the action of a renal ferment, was first suggested by Rosenblath (143). No doubt he was impressed with the frequent finding of necrotic arterioles in cases of malignant hypertension. The evidence of a circulating renal toxin (renin) in certain cases of hypertension requires that this proposition be reinvestigated. Winternitz *et al.* (180) have, in fact, succeeded in producing hemorrhage and vascular necrosis in the brains of experimental animals by removing the kidneys and then injecting extracts of kidney and testis.

A number of writers [Westphal & Baer (175), Schwartz (147), Scheinker (146), and Aring (12)] have asserted that spasm of an artery or an arteriole may initiate a series of events which culminates in brain hemorrhage Evidence of angiospasm in the brain comes from several sources. It is pointed

plantar reflexes are often extensor bilaterally. Rupture of the hemorrhage into the ventricles causes profound coma and may abolish all tendon and cutaneous reflexes. The cerebrospinal fluid is bloody and under increased intracranial pressure in more than 80 per cent of cases [Aring and Merritt (13)]. The features of brain hemorrhage that are usually so characteristic as to leave little doubt concerning diagnosis are: (*a*) the previously hypertensive status of the patient (*b*) the rapid progression of the neurological signs (*c*) the depth of the coma (*d*) the cerebrospinal fluid findings, and (*e*) the fatal termination within hours to days in over 90 per cent of cases. Dilatation of the pupil on the side of the lesion, loss of pupillary reflexes, stiff neck, bilateral Babinski signs, conjugate deviation of the head and eyes to the side of the lesion, and leucocytosis above 20,000 per c.mm. are frequent in brain hemorrhage and rare in brain infarction.

Pontine hemorrhage is the most rapidly fatal of any form of apoplexy; in rare instances it may cause death in 30 to 60 min.[4] Coma develops at once or within a few minutes Hemiplegia rapidly gives way to quadriplegia and segmental brain stem structures are disordered, e g. small or unequal pupils, ophthalmoplegia, unilateral paralysis of all parts of the face or unilateral facial anesthesia and corneal anesthesia on the side opposite the initial hemiplegia. The cerebrospinal fluid is invariably bloody-tinged We have observed rare cases in which hemorrhage was small and nonfatal; there was an initial disturbance of consciousness with ophthalmoplegia and sanguinous cerebrospinal fluid Cerebellar hemorrhage is seldom diagnosed during life. Rapidly-developing coma, bloody cerebrospinal fluid, and absence of hemiplegia have been recorded in most cases Sometimes the onset is more gradual with headache, dizziness, staggering, and vomiting.

Often these syndromes are not as precise as described in textbooks. One reason is that hemorrhage may extend from the pons up into the internal capsules or posteriorly into the cerebellum, or a cerebral hemorrhage may extend into the midbrain. Also, cerebral hemorrhage may cause a number of secondary or Duret hemorrhages in the midbrain and pons. It is noteworthy that massive brain hemorrhage, with its frequent tendency to enter the ventricles, causes far greater disturbance of consciousness than does the meningo-cerebral hemorrhage of an aneurysm or angioma.

Whereas little progress has been made in learning the cause and mechanism of brain hemorrhage, several interesting suggestions concerning treatment have been offered in recent years. Bagley (15), Craig & Adson (41), Handfast & Heimendahl (84), Guillaine & Joinville (82), Martelli (118), and Gross & Wechsler (81) have succeeded in surgically evacuating the blood clot. Aspiration of fluid blood resulted in prompt improvement and in some cases there was surprisingly little residual paralysis. However, in the few cases that have been selected for operation, the hemorrhage was small or of

[4] Apoplexy in any form is seldom the cause of sudden death. One does well to turn to the heart or lungs for explanation of death within seconds or minutes.

from their appearance in a microscopic section. Many of the current theories about brain hemorrhage have no pathological foundation whatsoever.

The location of the hemorrhage in 164 cases of hypertension and arteriosclerosis observed at the Boston City Hospital over a period of 10 years was as follows: in 68 per cent of cases it was in the region of the basal ganglia (lenticular nucleus, internal capsule and thalamus); in 13 per cent it was in the cerebellum; in 10 per cent it was in the cerebral white matter; in 7 per cent it was in the pons; and in 2 per cent it evidently arose within the ventricle, probably from the choroid plexus. These figures are in approximate agreement with those of Greenfield (79) and Boyd (21).

During this same 10 year period we observed 55 cases of hemorrhage in *individuals who had neither hypertension nor arteriosclerosis. In these cases* there was a saccular aneurysm, an angioma, a bacterial endocarditis with septic brain embolism, or a primary disease of the blood, i e , leukemia, pancytopenia, thrombopenic purpura, or hemophilia. These nonhypertensive hemorrhages are usually situated in the cerebral white matter and cortex or cerebellum rather than basal ganglia, and may be multiple. The aneurysmal hemorrhages were invariably meningo-cerebral, i.e., extending from the meninges into brain tissue. Thus, in a large pathological material one out of every three to four brain hemorrhages is due to some cause other than hypertension and arteriosclerosis. Brain hemorrhage in young normotensive individuals should always raise the question of an underlying vascular abnormality, a blood disease, or subacute bacterial endocarditis. The angioma, which probably accounts for not more than 3 to 4 per cent of cases of brain hemorrhage, may be so small that it may not be visible in an arteriogram and may even be overlooked postmortem. Margolis *et al.* (117) have recently reported several typical examples of small angiomas which were demonstrated only after careful microscopic examination of the walls of the brain hemorrhage and the clot. In our autopsy material approximately one out of 10 cases of hemorrhage, always of meningo-cerebral or meningo-cerebral-ventricular variety, was traceable to a ruptured saccular aneurysm

Little new information has been written about the clinical manifestations of brain hemorrhage since the publication of Merritt & Aring (120) in 1938. Although the syndromes produced by hemorrhage into the brain are [illegible] the
[illegible] hage
[illegible] im-
pairment of consciousness with confusion, stupor, and coma developing over a period of several hours. If the onset of coma is not instantaneous, there may be a complaint of headache and vomiting Hemiplegia and hemianesthesia are *invariably present Although they may develop gradually in some cases,* the paralysis is usually complete by the time the patient is examined. Breathing is stertorous and of Cheyne-Stokes type in later stages of the illness The level of tendon reflex activity on the hemiplegic side varies; it may be the same, slightly less or, rarely, greater than in the nonhemiplegic limbs. The

cases. Myocardial infarction with mural thrombosis occurred slightly less often in our autopsy material between the years 1942 to 1946. However, in a more recent statistical survey the order was reversed and myocardial infarction was more frequent than endocarditis In cases of coronary thrombosis there was a mural thrombus on the endocardium overlying some part of the myocardial infarct and embolism usually occurred a few days after the coronary occlusion. In a number of cases a stroke was the first manifestation of heart disease, the myocardial infarction having produced no symptoms.

All other types of brain embolism constitute no more than 5 to 10 per cent of the total cases. From time to time we have observed sporadic cases of brain embolism from thrombosis of carotid arteries, a thrombus in the superior thyroid artery after thyroidectomy, "marantic" endocarditis in cases of carcinomatosis, and from verrucous endocarditis in rheumatic fever and lupus erythematosus Fat embolism, air embolism, and amniotic fluid embolism have occurred infrequently in our material. The latter has been reported by a number of recent workers in cases of sudden death during parturition [Steiner & Lushbaugh (156) and Mallory *et al.* (116)], and we have observed one case of it with curled epithelial squamae in brain arteries.

Zuk & Elias (186) have shown that atheromatosis of aorta and carotid arteries can be the cause of brain embolism They have demonstrated crystals of cholesterol, similar to those seen in atheromas, in the center of brain emboli Convincing evidence is therefore offered that atheromatous material may extrude through the endothelium of an artery and be carried as an embolus to smaller branches of that artery. Since this was pointed out to us, we have observed cholesterol crystals in two emboli where it seemed reasonably certain that there was no chance of atheromatous material being displaced, postmortem, from the vessel wall into an intravascular clot.

Many pathologists are of the opinion that an atheromatous ulcer may also provide a nidus for the formation of a mural thrombus which may in turn undergo fragmentation and give rise to embolism [Duff & McMillan (49)] In three of our own cases we have found clots attached to atheromatous ulcers in the arch of the aorta and, in one, the tail of the clot had drifted into the left common carotid artery, a branch of which was occluded by an embolus

We have seen cases from time to time in which a brain vessel was definitely occluded by an embolus, as proved by microscopic section, yet no source could be demonstrated in the carotid artery, aorta, or left side of the heart. Some neuropathologists, i e, Wilson, Rupp & Riggs (179), suggest that these represent intravascular clots which develop during a period of stagnation of the blood and that such events are common during heart failure. The finding, however, of endothelial cells, fibroblasts or mononuclear cells, and disintegrating hematogenous cells in intravascular clots that have no attachment or oganization to the wall of the vessel, indicates to us that the clot had formed at least several days before it had lodged in that vessel. Admittedly, it is impossible in some instances to decide whether intravascular

only moderate size and the patient had already survived for several days in a stuporous or lightly comatose state. Papilledema had developed in some cases. Unfortunately, most cases are in such poor condition that they probably could not survive the operation. Considering the high mortality rate in hypertensive-arteriosclerotic brain hemorrhage one cannot but agree with Fazio (55) that neurosurgeons should be encouraged to extend their activities in this field. It is our impression that the diagnosis of brain hemorrhage can be made with certainty in most cases and that almost any reasonable procedure is worthy of trial in a disease that is lethal in more than 90 per cent of cases.

Brain Embolism

Brain embolism, both in experimental animals and in humans, has been intensively investigated in recent years Several controversial points have been clarified by these studies In the pathological material reported by Weiss & Davis (174), Kubik (104), and Fisher & Adams (61) embolism appears to be the most frequent cause of "stroke" or "shock." Furthermore, embolic occlusion of arteries occurs more often in the brain than in any other organ. Clinical pathological studies show that the great majority of emboli in the central nervous system produce symptoms, in contrast to other organs where embolic infarction is often silent. The fact also emerges that typical cases of brain embolism are often incorrectly diagnosed both by clinicians and pathologists. Furthermore, embolism may occur when there is no recognizable source and, to add to the difficulty of the problem, it has been our experience in some instances that even the most thorough examination of the brain may fail to disclose the embolus. The incidence of brain embolism in all statistical surveys is probably lower than it should be, and many of the cases which we have been forced to classify in the category of "undetermined cause" are probably examples of this condition

Several aspects of the subject of embolism have been discussed in recent publications: (*a*) the source of brain emboli; (*b*) the effect of embolic occlusion on brain tissue; (*c*) the criteria for diagnosis and; (*d*) newer methods of treatment.

Source of emboli.—Thrombi in the auricular appendage are the most frequent source of embolism, being responsible for more than half of the cases. The underlying heart disease is usually rheumatic or arteriosclerotic [Adams & Cohen (6)] There is auricular fibrillation in most cases. Sometimes, in cases with fibrillation, there is no source for the embolus in the heart or aorta. The relation of the fibrillation to embolism is then a matter of inference because the clinician can only assume that a pre-existing auricular fibrillation was causally related to the apoplectic incident, and the pathologist can but suppose that all the embolic material in the fibrillating auricle had been carried to its final destination in the smaller arteries

Thrombi from diseased heart valves in bacterial endocarditis was the second most frequent source of embolism, being found in one-fourth of the

and all other parts of the brain which are nourished by this vessel were pale. In these cases the embolus was found, not in the artery of supply to the whole infarcted zone, but in branches of that artery proximal to the anemic portions of the infarct. These relationships of embolus to infarct are shown in Table II. In some cases, all parts of the infarct are hemorrhagic and in these we have usually not succeeded in finding the embolus; in two cases it was possible only by microscopic examination to demonstrate embolic material in the most distal twigs of the involved artery.

From these findings it was postulated that the essential conditions for hemorrhagic infarction are ischemic necrosis of brain tissue with damage to small blood vessels, and later restoration of circulation to the infarcted zone under sufficient arterial pressure to rupture small blood vessels or to permit diapedesis from the engorged, highly permeable vessels. Embolism may create these conditions whereas thrombosis rarely does so. Embolic material may lodge in a vessel at a point of branching and arrest the circulation distally. Then, by fragmenting or shattering, it may be transported to more distal branches within the infarct The proximal portions of the infarct are exposed to the force of arterial blood pressure with extensive extravasation whereas the distal portions, whose vascular supply is still obstructed, remain pale or anemic. The suddenness of embolic occlusion probably induces local vascular spasm, as shown by Villaret & Cachera (167) in their direct observations of pial vessels of experimental animals through a brain window. In human post mortem material we have no means of assessing the relative importance of angiospasm in hemorrhagic infarction.

This theory of migratory embolism and intermittency of vascular occlusion explains why hemorrhagic infarction would rarely occur in thrombosis where the occlusion is more permanent and the thrombus is fixed in a certain segment of the vessel. It explains also the frequent finding of mixed hemorrhagic and anemic infarcts and either the failure to find the embolus in all cases of this type or the localization of the embolus in the more distal parts of the infarct.

Harvey & Rasmussen (86) were able to produce hemorrhagic infarction in two monkeys by occluding the middle cerebral artery for 50 min. and then removing the ligature They further showed that any manipulation of the middle cerebral artery resulted in a marked constriction of all the pial arteries over the exposed hemisphere and even in the distal part of the internal carotid artery The presence and extent of infarction varied with the duration of occlusion. Occlusions of 15 min or less produced only a temporary impairment of motor function and no demonstrable brain lesions No gross changes were seen after an occlusion of 30 min. duration Convulsions occurred in three animals following occlusions of 30 and 40 min Hain *et al* (83) have also studied hemorrhagic infarction in dogs after clipping different parts of the middle cerebral artery. They were successful in reproducing this lesion in the basal ganglia only if the clip were placed between the penetrating ganglionic branches. In both dogs and monkeys, temporary or perma-

clots have formed just before or after death or if the occlusive vascular process is one of thrombosis or embolism.

Effects of embolism on brain tissue—Pathologists, since the time of Cohnheim, have known that brain infarction produced by arterial occlusion may be either pale (anemic) or hemorrhagic. The hemorrhagic infarct consists of an ordinary softening of the tissue, the major portion of which is speckled by congested blood vessels and innumerable small hemorrhages These hemorrhages usually occur only in the gray matter (cerebral cortex or lenticular and caudate nuclei) and often become confluent. The blood changes color during liquefaction and the final stage of this lesion is a fenestrated cavity with orange-brown walls. The general architecture of the infarcted tissue is preserved, in contradistinction to massive brain hemorrhage where the tissue is replaced or displaced by homogeneous clot. In the pale infarct the tissue is soft, swollen, and the anatomical structures are poorly demarcated; later, liquefaction, necrosis, and finally cavitation become evident. There are no hemorrhages, except occasionally at the margins of the infarct, and vascular congestion, though usually present, is not as pronounced as in the hemorrhagic infarct.

The significance of these differences has been under debate for more than a century. Some pathologists, represented by Greenfield (80), assert that these are merely phases in the natural course of infarction, the hemorrhagic state always preceding the pale or anemic. Others have contended that brain infarcts may be of either type and the determining factor is the degree of venous stasis and height of venous pressure [Cobb & Hubbard (37), Evans & Scheinker (54)] Temporary arterial occlusion by prolonged angiospasm has been suggested by Westphal (176) as an explanation of hemorrhagic infarction whereas Fazio (56) has stated that diminution of arterial blood flow with subsequent stasis, dilatation, and dipaedesis is the principal mechanism.

Our own observations on hemorrhagic infarction [Fisher & Adams (62)] disclose that in the majority of cases brain embolism is the underlying factor. Excluding cases of obvious thrombosis of cerebral veins or venous sinuses and certain exceptional cases of internal carotid or basilar thrombosis, hemorrhagic infarction has been associated with embolism almost exclusively. In approximately 65 per cent of all cases of embolism the infarcted tissue is partially or completely hemorrhagic, and in the remainder it is pale or anemic. Hemorrhagic infarction has been observed occasionally in cases of temporal lobe-tentorial herniation with softenings in the temporal and occipital lobes and in a few cases of tuberculous meningitis with brain infarction. This association of hemorrhagic infarction with arterial embolism was known to Rokitansky and other early pathologists

In many of our cases of hemorrhagic infarction, part of the infarcted tissue was pale or anemic and part was hemorrhagic. In every instance, the hemorrhagic portion was proximal, i e, downstream or towards the heart, to the pale portion. Thus, the lenticular and caudate nuclei which are supplied by the first branches of the middle cerebral artery were hemorrhagic

and all other parts of the brain which are nourished by this vessel were pale In these cases the embolus was found, not in the artery of supply to the whole infarcted zone, but in branches of that artery proximal to the anemic portions of the infarct. These relationships of embolus to infarct are shown in Table II. In some cases, all parts of the infarct are hemorrhagic and in these we have usually not succeeded in finding the embolus; in two cases it was possible only by microscopic examination to demonstrate embolic material in the most distal twigs of the involved artery.

From these findings it was postulated that the essential conditions for hemorrhagic infarction are ischemic necrosis of brain tissue with damage to small blood vessels, and later restoration of circulation to the infarcted zone under sufficient arterial pressure to rupture small blood vessels or to permit diapedesis from the engorged, highly permeable vessels. Embolism may create these conditions whereas thrombosis rarely does so. Embolic material may lodge in a vessel at a point of branching and arrest the circulation distally. Then, by fragmenting or shattering, it may be transported to more distal branches within the infarct. The proximal portions of the infarct are exposed to the force of arterial blood pressure with extensive extravasation whereas the distal portions, whose vascular supply is still obstructed, remain pale or anemic. The suddenness of embolic occlusion probably induces local vascular spasm, as shown by Villaret & Cachera (167) in their direct observations of pial vessels of experimental animals through a brain window In human post mortem material we have no means of assessing the relative importance of angiospasm in hemorrhagic infarction

This theory of migratory embolism and intermittency of vascular occlusion explains why hemorrhagic infarction would rarely occur in thrombosis where the occlusion is more permanent and the thrombus is fixed in a certain segment of the vessel. It explains also the frequent finding of mixed hemorrhagic and anemic infarcts and either the failure to find the embolus in all cases of this type or the localization of the embolus in the more distal parts of the infarct.

Harvey & Rasmussen (86) were able to produce hemorrhagic infarction in two monkeys by occluding the middle cerebral artery for 50 min and then removing the ligature. They further showed that any manipulation of the middle cerebral artery resulted in a marked constriction of all the pial arteries over the exposed hemisphere and even in the distal part of the internal carotid artery. The presence and extent of infarction varied with the duration of occlusion Occlusions of 15 min. or less produced only a temporary impairment of motor function and no demonstrable brain lesions No gross changes were seen after an occlusion of 30 min. duration. Convulsions occurred in three animals following occlusions of 30 and 40 min. Hain *et al.* (83) have also studied hemorrhagic infarction in dogs after clipping different parts of the middle cerebral artery. They were successful in reproducing this lesion in the basal ganglia only if the clip were placed between the penetrating ganglionic branches. In both dogs and monkeys, temporary or perma-

nent occlusion produced only anemic infarcts in the cerebral cortex and white matter. As stated above, Broman (24) found that after experimental micro-embolism the level of arterial pressure was decisive in determining the extent of hemorrhage. Unless hypertension was produced by injections of epinephrine there were no hemorrhages in the softened tissues

From these experimental and pathological findings it is not surprising that the effects of embolic occlusion may be transitory, as shown so clearly in the report of Pickering (137). Embolic material may lodge for a few minutes in a large artery and then be carried to more distal branches before ischemic necrosis of tissue occurs. In one of our cases with hemiplegia, hemianesthesia, and aphasia lasting for only a few hours there was at autopsy two weeks later no evidence grossly or microscopically of a lesion in the appropriate regions of brain, and the only finding was a small infarct of the proper age in the lateral occipital region resulting from an embolus in a terminal branch of the posterior temporal artery. If arterial occlusion of less than 40 min. duration in the monkey will permit full functional recovery if relieved, a similar period of time may be required in order for infarction to occur in human brain tissue. Probably this depends on the relative degree of ischemia in the territory of the occluded vessel In our opinion, the statement of Globus and his associates (75) and Hicks & Warren (88), that there is no important difference between massive brain hemorrhage and hemorrhagic infarction, is not justified from the available pathological evidence.

In older writings it was said that hemiplegia occurring on the right side was presumptive evidence of thrombosis or embolism, while the fact of its occurring on the left side was presumptive evidence of hemorrhage. Remarks such as this and, also that embolism is more frequent in the left side of the brain, reappear in current publications. In our pathological material, the incidence of embolism is approximately the same in the two cerebral hemispheres This is also true of hemorrhage and thrombosis Jones (97) had conclusively settled this matter in 1910. The carotid artery and particularly the middle cerebral arteries are the usual sites of embolism; in approximately 80 per cent of our cases the embolus has been in these vessels

Clinical manifestations of brain embolism.—The extreme suddenness of onset, the occurrence of focal or generalized seizures, and deficits of brain function which vary according to the involved blood vessels and brain tissue are well known. As with thrombosis, coma may not occur, and if it does it is rarely as deep as in brain hemorrhage. The finding of a sanguinous cerebral spinal fluid has been reported in the clinical records of a few of our cases, but in the majority of cases the fluid was clear. As stated before, clinical manifestations of embolism are noted in nearly all cases of brain embolism, and considering the variety of nervous disorders that may be produced this group of cases offers a unique opportunity to observe the effects of embolic occlusion on the function of an organ A thorough clinical study of brain embolism has not been made.

Criteria for the diagnosis of brain embolism.—In a study of 57 cases of

brain embolism, Fisher & Adams (62) were able to find the embolus and to confirm the diagnosis by microscopic examination in 26 cases. In the remaining 31 cases the embolus was not found and the diagnosis was based on four types of evidence: (*a*) the demonstration of an embolus in some other part of the brain or in another viscera in relation to a recent infarct; (*b*) the existence of a source of embolism or the presence of auricular fibrillation; (*c*) the finding of recent infarcts in other vicsera where thrombotic occlusion of vessels is rare, i e. spleen, kidney; (*d*) the finding of multiple recent infarcts in the brain and the absence of significant atherosclerosis. The various combinations of these four factors are tabulated in Table II. The propriety of the diagnosis of embolism in some of our cases might be questioned, but we believe that collateral evidence is convincing in most instances

TABLE II

EVIDENCE OF 57 CASES OF BRAIN EMBOLISM

Anemic Infarcts	19
Embolus found proximal to infarct	14
Embolus not found but assumed	5
Source demonstrated in	4
Multiple visceral+Multiple brain infarcts	1
Hemorrhagic Infarcts	38
Embolus found	12
(In 8 distal to infarct)	
Embolus not found but assumed	26
Source+multiple visceral+multiple brain infarcts	5
Source+multiple visceral infarcts	7
Source+multiple brain infarcts	3
Source+only	3
Multiple visceral infarcts	1
Multiple visceral+multiple brain infarcts	1
Multiple brain infarcts without atherosclerosis	6

It is to be noted that in 14 of the 19 cases of pale or anemic infarction the embolus was found lodged securely at a point in an artery just proximal to the infarct, i.e downstream towards the heart In four of the remaining cases the infarct was either small or several weeks old and the embolus was not identified In only one case of a large fresh infarct were we unable to demonstrate the embolus and in this case the arteries in the neck had not been examined. In contrast, the embolus was discovered in only 12 of 38 cases of hemorrhagic infarction and in 10 of the 12 it was found distal to the place in the artery where it should have been to account for the whole area of infarction Often it was in a small branch within the infarcted tissue at the apex of a pale or nonhemorrhagic zone. In the other two cases, the diagrams which we had made were not sufficiently exact to be sure of the relation of the embolus to the infarct.

Our recent studies of the pathology of vascular disease corroborate the original impression that in cases of hemorrhagic infarction resulting from embolus, either the embolus is not found or is located in a more distal position than one would expect. It is therefore proposed that migratory embolism, and possibly transitory segmental vasospasm proximal and distal to the occlusion, are responsible for hemorrhagic infarction, and that the finding of a hemorrhagic infarct or the fenestrated brownish pigmented cavity of an old softening should always suggest the possibility of embolism.

Recent advances in therapy.—The role of vasomotor nerve fibers in the regulation of the caliber of intracranial arteries during focal ischemia of the brain has been debated. Leriche & Fontaine (109) and many others have stated that cervical sympathectomy, achieved by either a procaine block of the stellate ganglion or stellate ganglionectomy, resulted in improvement of such signs as hemiplegia and aphasia. The criticism has been made that such improvement could have occurred spontaneously. In the United States, after Gilbert & de Takets (73) and Volpitto & Risteen (170) popularized this technique, many neurologists and neurosurgeons have applied it to all types of apoplexy. Most of them have been unable to secure beneficial results except in rare cases. There are, in addition, several other objections to the procedure. Recent quantitative studies of cerebral blood flow by Naffziger & Adams (125) and Harmel *et al.* (85) have shown that stellate ganglionectomy does not alter the total blood flow to the brain. Furthermore, as has been pointed out by many neurosuregons and pathologists, the pial vessels in the region of an infarct are nearly always found in a state of dilatation probably because of the local action of tissue metabolites and, on theoretical grounds, it would seem doubtful if circulation could be much increased by stellate block. Lastly, such procedures may be hazardous if done by inexperienced physicians; pneumothorax and hemorrhage in the neck and, in one of our cases, a transfixion of the spinal cord have been accidently produced from time to time.

It is our impression that a decision as to the value of this procedure must await the verdict of a controlled scientific experiment. A few of the clinical case reports of temporary improvement after each procaine block which lasts only as long as the effect of the drug are impressive, but certainly in the majority of cases one can be sure that the procedure is worthless It must be admitted [Browne, Stern & Walker (26)] that the failure of the procedure to increase the total cerebral blood flow does not invalidate anatomic [illegible] Re-

[illegible]

sible procedure and a safe one if done by an experienced person. It could conceivably improve blood flow in an ischemic region or permit the distal migration of an embolus at a critical moment. The indiscriminate use of this procedure in all types of vascular disease must, of course, be deprecated.

ATHEROSCLEROSIS, THROMBOSIS AND ENCEPHALOMALACIA

Atherosclerosis of coronary, cerebral, renal, leg arteries, and aorta is the leading cause of death in the United States. The recognition of this fact has prompted an intensive investigation of the metabolic aspects of atherosclerosis. A major change in our conception of this condition has occurred in the past decade. Prior to that time opinion was divided as to whether atheroma formation was the result of a primary degenerative or aging change in the arteries, or of a disorder of lipoid metabolism. The former view was held by the majority of pathologists and only a few such as Leary (108) in this country supported the latter hypothesis. At the present time it seems to be generally conceded that atherosclerosis is a disorder of fat metabolism and that a better understanding of the formation, transportation, and storage of lipids is likely to afford an explanation of this disease.

Etiology and pathogenesis.—For a long time the experimental study of atherosclerosis was hampered by the fact that man is the only one of the mammals that develops this type of vascular disease. Then atherosclerosis was discovered to occur spontaneously in chickens and ducks, and, also, that it could be produced experimentally in rabbits and guinea pigs by the feeding of high cholesterol diets, and in dogs if cholesterol and thiouracil were given simultaneously. This experimental disease has been studied by many groups of research workers

At present, the following lines of experimental evidence are believed to support the metabolic hypothesis of atherosclerosis: (*a*) The pathological study of early human lesions and early experimental lesions has shown an almost identical morphology The earliest lesion consists of fatty flecks or streaks in the posterior wall of the thoracic aorta. The first microscopic change, according to Duff & MacMillan (49), is a swelling and metachromatic change in the ground substance of the intima followed by a deposit of fat droplets, (*b*) Chemical analyses of the lipids in early atherosclerotic lesions have demonstrated that they are of the same composition as the lipids of blood plasma, (*c*) In some diseases known to cause hypercholesterolemia such as diabetes mellitus, hypothyroidism, and familial xanthomatosis, the incidence of atherosclerosis is higher than in the general population as a whole; (*d*) An increase in macromolecular fat droplets has been found in the blood of humans who have atherosclerotic heart disease [Gofman and associates (78)]; (*e*) Other macromolecular molecules, such as the vinyl alcohols, result in intimal vascular deposits of the same material.

Several objections have been raised against the metabolic hypothesis. The fat of the older atheromas contains di-hydrocholesterol and not cholesterol in the form in which it occurs in the blood Then too, the blood cholesterol, though elevated in a few cases of atherosclerosis, has been normal in most instances. The lowering of dietary cholesterol has been shown to have little or no effect on blood cholesterol [Keyes *et al.* (101)], and finally, athero-

sclerosis in association with hypercholesterolemia is the exception rather than the rule.

Because of these inconsistencies, the whole subject of blood lipids, their nature, sources, mode of transport, life cycle, and excretion, is being re-examined. Already it has been learned that the lipids are actively synthesized in nearly all of the tissues, conjugated with proteins in the blood and tissues, and linked with one another. All of the major lipids of the blood, i.e. cholesterol, cholesterol esters, phospholipids, and fatty acids are found to be transported in the form of giant molecules which can be separated by an ultracentrifuge technique. Those of small size, 10 to 30 Svedborg flotation units, are said by Gofman *et al.* (78) to correlate with atheromatosis. The latter authors believe these molecules represent merely a stage in a metabolic cycle whereby molecules of larger size are transformed successively into ones of smaller size and finally to cholesterol. The thyroid gland proves to be one of the regulators of the metabolism of cholesterol and probably phospholipids as well. At least two lipotropic agents, choline and inositol, are believed to be engaged in mobilizing and removing lipids from the atheromatous lesion. The essential factors underlying the deposit of these fatty substances in the walls of blood vessels are not known.

Many of the reported findings in recent experiments on fat metabolism in human cases of atherosclerosis require corroboration. Application of these new data to the clinical study of cases of atherosclerosis have been few and are difficult to control, since atherosclerosis may exist in individuals who have no symptoms of vascular disease. The most that can be said at present is that the data are interesting and suggestive. The reader who seeks further details on the metabolic aspects of atherosclerosis is referred to the *American Journal of Medicine*, 1951, and particularly to the article of Davidson (45).

The pathology of atherosclerosis.—The publications of Leary (107, 108) and of Duff & MacMillan (49) provide us with the most complete descriptions of the morphology of the atherosclerotic lesion. An observation surprising to most physicians is the early onset of atherosclerosis. Fatty streak and flecks in the aorta are reported in 95 per cent of cases less than 16 years of age. The aorta is involved first, the coronary artery somewhat later, and the cerebral arteries still later. Several reports of coronary thrombosis in the third decade of life have appeared in recent years. We have seen thrombosis of brain arteries in the fourth decade of life but more often this does not occur until the fifth and sixth decades. The earliest lesion in the brain arteries, like that in the coronary arteries, is a metachromatic staining of the ground substance of the intima followed by an infiltration of blood lipids, first in the form of fine droplets [Duff & MacMillan (49)] or as macrophages [Leary (107)]. In most of the early lesions some fat is seen in macrophages and in stellate and spindle-shaped mesenchymal cells. The fatty deposit is always situated next to the internal elastic lamina in the deep layers of the intima. Fibrosis, presumably as a reaction to the fat, occurs later. The lesions are covered or capped on the inner surface by fibrous tissue which has the ap-

pearance of small, white or grayish plaques on the lining of such vessels. Macrophages later disintegrate, leaving a pultaceous mass of lipids and necrotic cellular debris. This is known as the atheroma In these lesions cholesterol-ester crystals may precipitate, and eventually calcification occurs. The ultimate fate of such lesions is variable. Some are resorbed, all of the fat disappearing, an eccentric lamina of fibrous connective tissue being the only residue. Or, the atheroma may spread laterally and coalesce with other lesions of similar type. The internal elastic lamina adjacent to the atheroma may rupture and part of the muscular coat may be destroyed. Again, the atheroma may rupture through the endothelium, discharging its grumous content into the blood stream and leaving an ulcerated surface devoid of endothelium. A thrombus may form on this ulcer. Carmichael (31) has demonstrated gross defects in the muscular and elastic coats of the atheromatous cerebral vessels where the atheroma has eroded the internal elastic lamina and destroyed the media. Vascularization of the atheroma by capillaries often occurs, and from the studies of Patterson (133) and others, these new vessels may later rupture giving rise to an intravascular hematoma. The latter will narrow or occlude an already atheromatous vessel, and by destroying the endothelium may lead to thrombosis In any one case, the co-existence of acute and chronic lesions is further proof that atherosclerosis is a chronic disease and that arterial thrombosis is merely a late or terminal complication Serious damage to the human organism usually results from thrombosis of coronary or cerebral arteries with focal ischemia or infarction of tissues There may also be progressive damage to kidneys with resulting hypertension and with all of the additional complications which it entails.

Few studies have been made of atherosclerosis of cerebral arteries. The last references that we have been able to find on the subject are the papers of Wolkoff (182) in 1933, and Seguro (148) in 1940. Our own observations are in essential agreement with theirs Atherosclerosis is most frequent in the first part of the internal carotid artery just above the bifurcation of the common carotid, and in the sigmoid portion of the internal carotid, in the first 3 to 4 cm of the middle cerebral, in the anterior cerebral artery just proximal and distal to the anterior communicating artery, and in the vertebral and basilar and proximal parts of the posterior cerebral arteries. These deposits form first at junctions of arteries and coalesce, as was mentioned above in the discussion of the aorta and coronary arteries. The process of atheromatosis undoubtedly weakens the vessel wall and one commonly sees extreme dilatation and elongation of an artery such as the basilar. These segmental dilatations are fusiform in shape and hence are called fusiform arteriosclerotic aneurysms. The internal carotid and vertebral arteries not infrequently calcify. This is because of calcification of atheromatous lesions and not to Monckeberg's calcific sclerosis In the more advanced stages, especially in hypertensive patients, atheromas appear in the smaller meningeal branches of the cerebral and cerebellar arteries and in the perforating lenticulostriate branches. The smallest brain artery in which we have seen a definite

sclerosis in association with hypercholesterolemia is the exception rather than the rule.

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the small vessels to be involved when hypertension and atherosclerosis coexist. The nature of the vascular lesions in the small arteries responsible for these small cavities has never been established. This information can only be obtained by serial sections of the arteries leading to such cavities.

Large brain arteries were found to have become thrombosed in only 11 per cent of our cases of vascular disease. The internal carotid, vertebral, basilar, and middle cerebral arteries are affected most frequently but any one of the cerebral and cerebellar arteries may become occluded. The multiple small cavities in basal ganglia and pons (*état lacunaire*) are about twice as frequent (19 per cent) as large infarcts; occlusions of small and large arteries co-exist in many of these cases. Necrosis of an atheroma with damage to the endothelium or intramural hemorrhage has been found in a number of thrombosed arteries in our series, but in others the cause of the thrombus was not ascertained by random microscopic sections

Clinical manifestations.—The clinical manifestations of atherosclerosis of the brain are discussed under the heading "Arteriosclerotic Brain Disease" in all of our standard textbooks Usually such discussions are based on the writers' personal experience with a few cases of thrombosis of major arteries and provide only a limited view of the disease. Alvarez (11) has recently called attention to some of the minor strokes that occur in arteriosclerotic patients but offers no pathological data Woltman (184) presented a brief résumé of the symptomatology of cerebral arteriosclerosis in which certain features other than apoplexy were stressed. He remarked on the high incidence of weakness, dizziness, unsteadiness, difficulty in walking, increased emotionality, forgetfulness, and change in personality Spastic weakness, ataxia, and paresthesias with signs of bilateral affection of pyramidal tracts and posterior columns were observed in a considerable number of cases [Woltman (183)] We have been unable to find a clear account of the varied clinical manifestations as they occur in all phases of the disease This could only be done by reviewing the histories of a large series of cases in which the diagnosis had been established by careful postmortem examination. Complicating factors such as hypertension, myocardial disease with brain embolism, and renal disease would add to the difficulty of the task

The intermittency of symptoms prior to the development of thrombosis is one of the remarkable features of atherosclerosis, especially when it affects the carotid and the vertebral-basilar arteries. No satisfactory explanation of this phenomenon has been forthcoming The deficit of nervous function which follows upon occlusion of a brain artery depends of course on the structures which are involved. The onset of symptoms is always abrupt as with all types of vascular disease of the brain, but there may be some progression in the clinical picture for several hours and saltatory advances with development of new symptoms may continue for two or three weeks. Improvement invariably occurs if the patient survives the apoplectic attack The onset is often less sudden than in brain embolism; and, unlike massive brain hemorrhage, coma is less frequent and if it occurs is less deep and progres-

atheroma is approximately two-tenths of a mm., though as pointed out by Wolkoff (182) the presence of fatty material in the intima of hyalinized vessels is not infrequent It is our impression that the smaller arteries are more often affected in hypertensive and in diabetic individuals. Scattered fatty macrophages may be seen in the Virchow-Robin spaces around arterioles and capillaries in both normal and arteriosclerotic brains, but since these are so common in other conditions they cannot be related to atherosclerosis As pointed out by Carmichael (31) destruction of the internal elastic lamina and media by atheroma is more frequent in the brain arteries than the coronaries. Local factors unquestionably influence the localization of the atherosclerotic plaques. The level of the arterial pressure is of importance. Atherosclerosis is more frequent and severe in hypertensive than in normotensive individuals Atherosclerosis of the pulmonary veins is found most often in individuals who have had left-sided heart failure. Wilens' (178) reports are particularly informative on the question of orthostatic influences on atherosclerosis.

Recent experimental studies of atherosclerosis have not proved to be particularly enlightening. Altschul (10) has shown that the feeding of high cholesterol diets to animals results in atherosclerosis of aorta and coronary arteries but not of the brain arteries. He also observed collections of foam cells in and around the small blood vessels of the hypothalamus, the leptomeninges, and the pineal gland. Also, atheromatosis of the choroid plexus was produced. One may conclude from these studies, and from observations of human cases as well, that the brain arteries are generally less susceptible to atherosclerosis than the aorta and coronary arteries. In human pathological material, however, exceptions are not infrequent, and we can recall several cases where there was severe atherosclerosis of brain arteries and only slight involvement of the coronary arteries There is need of further morphological studies of the brain in human cases of atherosclerosis. An attempt should be made to establish the relationship between the atheromatous lesions of the large brain arteries and the intimal deposits of fat and hyalinization in the small ones. Also, the relationship of atherosclerosis and hyaline and hyperplastic arteriosclerosis in the brain arteries to retinal vascular changes needs further clarification. Alpers, Forster & Herbut (9) have attempted this correlation but they do not differentiate the different types of arteriosclerosis in their report

Atherosclerosis damages the brain by causing thrombosis of nutrient arteries. Occlusion of very small arteries results in small softenings which eventually become fenestrated cavities. The latter are especially common in the basal ganglia and pons. In our own pathological material lesions of this type were usually multiple and were the only pathological finding in approximately 20 per cent of the cases of vascular disease As pointed out by Fisher (58), these multiple small cavities occur almost exclusively in hypertensive individuals, the only exceptions being the cases with diabetes mellitus This may only reflect the greater severity of atherosclerosis and the tendency for

content of oxidase. His results explain the distribution of lesions in the brain in anoxic encephalopathy and possibly hypoglycemia The regions of the cat's brain that are the least vascular and have the lowest oxidase content are the lamina radiata of the archicortex (Ammon's horn) and the globus pallidus In the parietal cortex laminae III and IV are the most vascular and the other laminae are about equal. The cerebellar cortex is about the same as the parietal lobe cortex. The lateral geniculate body is the most highly vascularized structure in the brain. Pfeiffer (135) has made the most thorough study of the vascularity of the human cortex and published his findings in a beautifully illustrated monograph. Abbie (2) and Shellshear (150) have described the vascular supply of the visual pathways and the latter remarked on the constancy of the vascular arrangements in the different mammals and in humans. The papers of Foix (63) and Walker (172) should be consulted for the vascular supply of the human thalamus, and those of Alexander (7), Alexander & Suh (8), Foley, Kinney & Alexander (68) and Finley (57) for the striatum, pallidum, and hypothalamus. Cobb & Talbot (38) have studied the capillaries of the cerebral cortex. The veins of the medulla and pons are the subject of an anatomical report by Berner (19), and Clark (35) has described a special vascular mechanism in relation to the great vein of Galen. Vander Eecken & Adams (165) have investigated the meningeal arterial anastomoses of the brain Some of the more common of these vascular syndromes have been summarized by Adams & Cohen (6) and more recently by Tichy (163).

The examination of humans whose brains have been suddenly disordered by occlusion of a blood vessel provides for the neurologist a unique opportunity to learn about the function of the brain. No other disease destroys certain areas with such precision and at the same time leaves other parts of the nervous system undisturbed. The value of accurate observation and recording of neurologic syndromes caused by brain infarction and later a careful correlation of the clinical with the pathological findings cannot be overemphasized In the past much of what we have learned about the nervous system has been acquired by taking advantage of these "experiments of nature."

Methods of examination of the brain in cases of vascular disease have improved in recent years but still leave much to be desired. Special methods must be employed if clinico-pathological correlation is to be reasonably exact, and failure to employ them has resulted in many inaccurate reports about occlusive vascular disease of the brain Hultquist (91, 92) has taught us the importance of testing the patency of the carotid and vertebral arteries in the neck and at base of skull. In a few years he discovered nearly a hundred cases of internal carotid thrombosis by dissection of these vessels. We have systematically checked their patency by the injection of water or colored solutions into the cervical portions of these arteries and have dissected them if an obstruction was encountered. Upon removal of the brain, the large arteries should be dissected and the patency of any suspicious occlu-

sive. The cerebrospinal fluid is invariably clear and under a normal or slightly increased pressure. The total protein content is normal or in the 40 to 100 mg. range The mortaltiy rate is much lower than brain hemorrhage; only a small percentage of patients die during the first attack of the disease. It may be impossible to distinguish thrombosis from embolism of brain arteries

Treatment.—No progress has been made in the treatment of atherosclerosis of brain arteries. The few reports of the effect of low-cholesterol or low-fat diets have been concerned only with coronary artery disease. In the management of the patient with a thrombosis of a brain artery one must depend on the use of supportive measures alone. There are no critical data on the value of anticoagulants or vasodilator drugs. Information of this type is, of course, difficult to obtain because of the variable and unpredictable course of the disease. Stellate ganglion block with procaine has been of no value in the cases which we have seen and the rationale as well as the objections to the procedure have already been discussed. Damage to the brain tissue probably occurs within a few minutes of vascular occlusion and little can be accomplished thereafter except the prevention of further thrombosis. The theoretic possibility of improving collateral blood supply to an ischemic area has been explored in animals by German & Taffel (72), who grafted cranial muscles to the denuded cerebral cortex of dogs. Although anastomoses between the pial and extracranial vessels did form, the method is obviously not applicable to humans.

Vascular Syndromes, Mechanisms of Apoplexy and Techniques of Clinico-Pathologic Study

The student or physician who seeks to acquire competence in this field of vascular disease must acquire a special knowledge of neurovascular anatomy that is seldom presented adequately in our textbooks of anatomy. Nevertheless, the clinical syndromes resulting from the occlusion of the cerebral and cerebellar arteries are well known. Each of the major brain arteries and the territory which they supply has been carefully worked out and the associated clinical manifestations have been accurately described. Also, the arterial supply and the venous drainage of all the important nuclear structures of the brain have been described. The writings of Beevor (17), Shellshear (150), Stopford (155), Foix and associates (64, 65, 66), and Abbie (1, 2, 3) should be consulted for information about the cerebral and cerebellar arteries. Hultquist (92), Moniz (122), Fisher (59), and Elvidge & Werner (51) have reported on the pathology and clinical effects of occlusion of the internal carotid artery and Foix & Hillemand (66) and Kubik & Adams (105) on the effects of basilar artery occlusion.

A few remarks concerning some of the more recent of these publications may be of interest to the physician and the student of neurological disease. The vascular supply of the cerebral cortex in mammals and lower forms has been presented in a series of papers by Craigie (42), and Campbell (30) has correlated the variations in vascularity in different parts of the brain with

secting microscope. In cases of hemorrhagic infarction, however, it is usually not possible to find the occluded material proximal to, or on, the cardiac side of the infarct, though often it will be seen in arteries within the infarct. Nonetheless, in our estimation these latter cases are a result of vascular occlusion. We have seen very few cases where no explanation could be found for a large, recent, pale brain infarct.

The common clinical problem of transitory hemiplegia or aphasia in a patient with disease of the heart and blood vessels has its solution in several different vascular mechanisms. It can be shown at autopsy that the prompt recovery of function was due to the fact that the nervous structures in question were situated at the margin of the ischemic zone and that a hemodynamic readjustment, usually operating through the system of capillary anastomoses, was adequate to restore the circulation. Migration of embolus before infarct necrosis occurred can at times be demonstrated. Hemiplegia may occur during a state of circulatory collapse and disappear when the arterial pressure returns to normal, and at autopsy stenosis or a silent thrombosis of an artery may be demonstrated. And finally, we have observed a number of puzzling cases, usually with disease of vertebral and internal carotid arteries, in which there have been repeated, stereotyped, transitory ischemic attacks, i e. hemiplegia with carotid artery affection or dysarthria, dizziness, blindness, or hemiplegia with vertebral artery involvement Forty or 50 such attacks may have occurred in as many days leaving no residual signs. Finally, the vessel becomes thrombosed and the patient dies. At autopsy only a recent thrombus and infarction were demonstrated. No explanation of these attacks can be obtained by post mortem examination. In some cases a postural hypotension, induced when the patient arose from a recumbent position, has been suggested by the history, but we have been unable to reproduce the attack by putting the patient on a tilt table [Victor & Adams (166)] Whether the extracranial portions of the internal carotid or vertebral arteries are capable of a far greater degree of spasm than is known to occur on the intracranial vessels cannot be decided from our data

It is our impression that spasm of the brain arteries does occur, but always in relation to some type of vascular disease and never as the primary event. Vasospasm probably should not be accepted as the whole explanation of any type of apoplexy.

Sunderland (160) has recently brought another aspect of neurovascular anatomy to our attention, that of the relations of the cranial nerves to the main branches of the vertebral, basilar, and carotid arteries. He illustrates several anomalous arrangements of vessels which had resulted in compression of or displacements of cranial nerves. No clinical data are given, but the possibility of this being the cause of some of the isolated and unexplained cranial nerve palsies in arteriosclerotic patients is suggested. Denny-Brown & Foley (47) have recently reported a pathological case in which an atherosclerotic basilar artery exerted direct pressure on cranial nerves and also interfered with the circulation to the brain stem.

sion should be tested by injection of water or colored solutions. Gelatin or barium solutions can be injected at this time in certain types of cases, but there is always some risk of dislodging an embolus. After formalin fixation the relationship of infarcts to occluded arteries should be determined. Transverse sections of occluded arteries are preferable to longitudinal sections and representative blocks should be examined under the microscope, at more than one level if possible.

By searching for occluded vessels and plotting the relationship of the occlusion to the ischemic brain lesion it is possible to demonstrate the effects of a number of hemodynamic mechanisms which appear to operate immediately upon occlusion of a brain artery. The efficiency of the circle of Willis as an important source of collateral blood supply for occlusions proximal to the circle (preWillisian, i e. between the heart and circle of Willis) can in this way be demonstrated and, also, a series of meningeal anastomotic loops between the cerebral and cerebellar arteries can be shown to function under these conditions [Vander Eecken and Adams (165)]. A rich plexus of capillary anastomoses represents the third system of collateral vessels. Each of these systems of anastomotic vessels serves under certain conditions to counteract the effects of focal ischemia.

By clinical and pathological study of cases of human brain infarction, it can be shown that thrombosis of a cerebral or cerebellar artery may occur without infarction This has been recorded by Pagniez (131), Claude & Cuel (36), Ley (110), and Vander Eecken & Adams (165), but it is rare. It usually happens when a vertebral, carotid, or anterior cerebral artery is occluded proximal to the circle of Willis, the latter effectively shunting blood into the cerebral arteries Infarction of the brain may also occur without thrombosis. This latter condition, designated in medical writings as "infarction without vascular occlusion," has been the subject of much controversy for the past hundred years. Isolated cases have been reported by several pathologists [Westphal (176), Foix & Hillemand (67), Scheinker (146), Hicks & Warren (88), Neuburger (126)]. The latter has reported a remarkable case of apoplexy which occurred thirty minutes after a head injury. At autopsy there was a softening in the brain without vascular occlusion. The possibility here of a thrombosis of the carotid artery in the neck could, possibly, have escaped notice. Infarction without thrombosis may occur, as in one of our cases, when arterial hypotension from a visceral hemorrhage has reduced the circulation through a stenotic, arteriosclerotic artery. We have observed similar accidents in elderly patients whose arterial pressure fell during operations for tic douloureux Denny-Brown (46) has recently reported examples of this condition Hicks & Warren (88) have stated that in a large proportion of their cases brain infarction without vascular occlusion has been found, and that vascular spasm has been the cause of infarction. Our experience has been somewhat different. We have found occlusions, either thrombi or emboli, in over 90 per cent of cases of anemic or pale brain infarction, by examining the arteries in the neck and in the brain vessels with a loupe or dis-

found in some cases, and has been the cause of death Arteriolosclerosis is a common finding in all cases of chronic renal disease but not in those resulting from acute glomerulonephritis, toxemia of pregnancy (eclampsia), or polyarteritis nodosa where long-standing hypertension has not existed This vascular change which consists of hyperplasia of endothelial cells, hypertrophy of media, intimal hyalinization, and splitting of the internal elastic lamina is a consequence of the hypertension and not an essential part of the pathology of hypertensive encephalopathy. Necrotizing arteriolitis, similar to that found in the kidney, can be demonstrated in the retina and the brain in many but not all of the cases This pronounced alteration in the small vessels is closely related to the petechial hemorrhages in the gray matter, and to perivascular exudates and miliary infarcts ranging from .1 to .2 mm. in diameter These are identical with the hemorrhages and exudates of hypertensive retinopathy. The edema of the brain tissue occurs in cases with large numbers of these lesions. The edema is diffuse but uneven; the unevenness is from a greater affection of tissue around the small vessels Rosenberg (142) has described the neuropathology in a series of cases of malignant hypertension and Fisher & Adams (62) have reviewed the findings in a series of fatal cases of malignant nephrosclerosis Moritz & Oldt (124) have provided us with one of the most complete and carefully controlled studies of the arterioles of the brain The most authoritative report on the retinal lesions which are an almost invariable part of this disease is that by Friedenwald (71).

In our pathological material apoplexy, regardless of its duration, has been traceable either to atherosclerotic thrombosis with infarction or to hemorrhage, and rarely to embolism An increased permeability of the brain vessels and a breakdown of the blood brain barrier [Broman (25)] is reflected in the high cerebrospinal fluid protein, which in a few of our cases has exceeded 200 mg per cent

There is no doubt, in our opinion, that hypertensive encephalopathy or pseudouremia represents a unique vascular syndrome Its relation to renal disease is yet to be elucidated, but in all probability the necrotizing and alterative arteriolar lesions result from some toxin elaborated by the damaged kidney in the presence of severe hypertension Alterative and necrotizing arteriolar lesions with petechial hemorrhages, perivascular exudates, and miliary infarcts represent the underlying pathological process and, if severe, result in brain swelling It has been stated that elevation of the hydrostatic pressure in the brain arteries during crises of hypertension causes brain edema, but this is not a satisfactory explanation in our opinion. In most instances, this clinical syndrome can be distinguished from true uremia in which headache and convulsions are infrequent and nonprotein nitrogen values reach high levels In many cases of malignant nephrosclerosis both conditions may occur terminally. The essential mechanism of the crises of hypertension and of the arteriolar changes in the kidneys, brain, and retinae has not been determined.

HYPERTENSIVE ENCEPHALOPATHY AND PSEUDO-UREMIA

There is greater ambiguity in the thinking of the average physician concerning the nature of hypertensive encephalopathy than any other form of vascular disease. Part of the difficulty in comprehending the nature of this condition arises as a consequence of inexact definitions of the term hypertensive encephalopathy. The term sounds well and seems to have captured the attention of the medical profession. There are some who apply it to every type of hypertensive vascular disease, whether embolic, thrombotic, or hemorrhagic, and others reacting against this tendency deny its existence as a special disease entity. One must turn back many years to the writings of Volhard & Farr (168), Oppenheim & Fishberg (129), and Keith & Van Wagener (98) for reliable information on this subject. They inform us that there is a special clinico-pathological entity that should be set apart from all other forms of vascular disease and from uremia. Volhard (169), in his only English paper on the subject of pseudouremia, offers an unexcelled description of the syndrome To him, it is an acute or subacute disorder of the nervous system developing in individuals with severe hypertension and renal disease, usually malignant nephrosclerosis, but in some instances acute glomerulonephritis or chronic pyelonephritis. Severe headache, convulsions, amaurosis, mental confusion, stupor or coma, and in some cases transient focal neurological signs such as hemiplegia, hemianesthesia, or aphasia are the main constituents of this syndrome These symptoms occur during the last weeks or months in the life of the hypertensive patient. Volhard attributed them to the effects of ischemia, either general or local, and noted that they are closely related to the vascular crises of Pal (132), in which there is a sudden elevation of arterial pressure with or without neurological symptoms. Although related in some obscure manner to renal disease, they are not a result of uremia. There is often only a slight elevation of nonprotein nitrogen values at the time when the neurological symptoms occur, and renal acidosis is absent in most cases There has been difficulty in deciding which of these many symptoms are to be included in the hypertensive or pseudouremic syndrome. Nearly all clinicians are agreed that headache, impairment of consciousness, and convulsions are dominant features but there is less uniformity of opinion concerning transient hemiplegia, aphasia, and amaurosis. Pickering (137) has pointed out, and everyone working in this field of vascular disease would assent to this view, that embolism and even thrombosis of brain vessels may cause transient focal neurological signs by mechanisms that we have already discussed in the previous section.

The pathology of hypertensive encephalopathy is equally confused. Original reports that the brain showed no pathological change or only swelling are inaccurate Certainly the most striking gross change is brain swelling or edema. This is evident from the increase in total weight of brain, the flattening of surfaces, the smallness of ventricles, and sometimes herniation of the cerebellum through the foramen magnum Massive brain hemorrhage is

found in some cases, and has been the cause of death. Arteriolosclerosis is a common finding in all cases of chronic renal disease but not in those resulting from acute glomerulonephritis, toxemia of pregnancy (eclampsia), or polyarteritis nodosa where long-standing hypertension has not existed This vascular change which consists of hyperplasia of endothelial cells, hypertrophy of media, intimal hyalinization, and splitting of the internal elastic lamina is a consequence of the hypertension and not an essential part of the pathology of hypertensive encephalopathy. Necrotizing arteriolitis, similar to that found in the kidney, can be demonstrated in the retina and the brain in many but not all of the cases This pronounced alteration in the small vessels is closely related to the petechial hemorrhages in the gray matter, and to perivascular exudates and miliary infarcts ranging from .1 to .2 mm in diameter. These are identical with the hemorrhages and exudates of hypertensive retinopathy. The edema of the brain tissue occurs in cases with large numbers of these lesions. The edema is diffuse but uneven; the unevenness is from a greater affection of tissue around the small vessels Rosenberg (142) has described the neuropathology in a series of cases of malignant hypertension and Fisher & Adams (62) have reviewed the findings in a series of fatal cases of malignant nephrosclerosis Moritz & Oldt (124) have provided us with one of the most complete and carefully controlled studies of the arterioles of the brain The most authoritative report on the retinal lesions which are an almost invariable part of this disease is that by Friedenwald (71)

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Aneurysms and Vascular Malformations

Saccular or congenital aneurysms of brain arteries and the vascular malformations have received more attention in recent years than any other form of vascular disease. The remarkable frequency of developmental anomalies of brain arteries is now well established. Probably no other organ shows a higher incidence of such lesions. The clinical manifestations and the pathology of these conditions were carefully described during the early years of the twentieth century To Symonds (162) is due much credit for defining the clinical syndromes produced by saccular or congenital aneurysms. It was he, more than any other clinician, who demonstrated that the diagnosis of aneurysm could be made with reasonable certainty during life. The general clinical and pathological aspects of the subject have been reviewed fully by Richardson & Hyland (140), and the surgical therapy has been outlined by Dandy (44). Cushing & Bailey (43) have rendered similar service with their fine monograph on vascular malformations of the brain, and Lindau (112) described clearly the hemangioblastomatous cysts of the cerebellum and the other anomalies in the syndrome to which his name has been attached.

Saccular aneurysms.—These congenital aneurysms resemble small berries or little sacs and are usually situated at the crotch of a bifurcating artery. They vary in size from a few millimeters to several centimeters in size. All are situated on the surface of the brain, in the meninges, and when they rupture the hemorrhage is always in the subarachnoid space The majority of these aneurysms are on the circle of Willis or the main cerebral arteries arising therefrom. They are far more frequent on the carotid than the vertebral and basilar arteries. This type of aneurysm is easily distinguished from the fusiform atherosclerotic aneurysm which does not rupture, but instead undergoes thrombosis with resulting infarction of brain and occasionally, if large, may compress cranial nerves. Syphilis is hardly ever a cause of aneurysms of brain vessels.

The pathology in the brain created by these aneurysms consists of diffuse subarachnoid hemorrhage, and in some cases meningo-cerebral hemorrhage, i.e subarachnoid hemorrhage that ruptures through the cerebral cortex into the substance of the brain and rarely into the ventricles as well Infarction of the brain tissue, often hemorrhagic, in the distribution of the vessel bearing the aneurysm is frequent, in some cases it is certain that a hemorrhage has occurred into brain tissue that had become softened at the time of a previous subarachnoid hemorrhage Presumably the softened brain tissue offers less resistance to the extension of the subarachnoid hemorrhage [Globus & Strauss (76)] than normal tissue The explanation of the ischemic necrosis of brain tissue is uncertain Thrombosis in the aneurysm and the vessel on which it is situated are seldom observed. Either lowering of intra-arterial pressure, or segmental spasm in the diseased artery may be of importance. Gradual expansion of the aneurysm, both by dilatation and by frequent small ruptures of the wall with organization and accretion of blood

clot, may occur. Some aneurysms reach several centimeters in diameter and compress structures at the base of the brain.

Three clinical syndromes have been defined. The most frequent is that of spontaneous subarachnoid hemorrhage which is manifested by the abrupt onset of severe headache, nausea and vomiting, and stiffness of the neck, and sometimes impairment of consciousness or a seizure. Fever, occasionally glycosuria, and rarely albuminuria follow within a day or two Somewhat less frequent is the syndrome of meningo-cerebral hemorrhage in which hemiplegia or aphasia, hemianesthesia, or homonymous hemianopia are added to the symptoms of meningeal irritation. This may be difficult to distinguish from brain hemorrhage were it not for the retention of consciousness in many of the cases of aneurysm Subarachnoid hemorrhage is about twice as frequent as meningo-cerebral hemorrhage. The syndrome of an expanding aneurysm at the base of the brain which simulates a brain tumor is relatively infrequent, but has become widely known through the papers of Jefferson (95, 96).

The theory that the saccular aneurysm is the result of a congenital malformation of blood vessels had its origin in the writings of Eppinger (53), and was corroborated by the work of Forbus (70). All workers have since confirmed that the media in the wall of the aneurysm is deficient, but there is is still some uncertainty as to whether or not this represents a congenital defect, and whether the accompanying deficiency of the internal elastic lamina is congenital or is secondary to expansion or some other process. The significance of this medial lesion is questioned by Carmichael (31) who points out that medial defects may occur either as developmental faults or as a consequence of atherosclerosis. Also, he noted that gaps in the media may occur in a rather large proportion of cases without aneurysms.

In order better to understand the development of these malformations several new studies of the embryology of the brain vessels have been undertaken by the following: Bremer (22), Moll (121), Padget (130), Streeter (158) and Sugar (159). They affirm that the main arteries of the brain arise from a complex meningeal vascular network and the development of these arteries has been followed all through embryonal and fetal life. Some aneurysms, particularly those which are found on unbranched segments of an artery, have been traced to a failure of regression of some particular part of this network. The role of faulty development in the causation of aneurysms appears therefore to rest on a firm basis However, the high incidence of atherosclerotic changes in them, over 40 per cent in McDonald & Korb's series (119), and the high incidence of rupture in late life (average age 50 years), indicates that degeneration of the vessel with age or as a result of vascular disease may further weaken the arterial wall and contribute to the final rupture

The introduction of angiography (x-ray of the brain after injection of the carotid or vertebral arteries with radio-opaque fluid) by Moniz (122, 123) has provided clinicians with a technique that has facilitated diagnosis and

has encouraged the development of more definitive methods of treatment. Several useful atlases showing the location and appearance of the major arteries in x-rays have been published [Engeset (52), Gross (81), Lima (111), Wechsler & Gross (173) and Wickbom (177)], among others, have reviewed the clinical applications of angiography in the field of vascular disease.

The first comprehensive statement of the neurosurgical treatment of aneurysms was presented by Dandy (44) in a beautifully illustrated monograph. Poppen (138) and several other neurosurgeons have since placed on record large series of cases treated by several different methods such as the ligation of the carotid artery in the neck, the ligation of the vessel on either side of the aneurysm, the ligation of the neck of the aneurysm, or total excision of the aneurysm. The indications for these different surgical procedures are reviewed in Poppen's paper, but they must still be regarded as somewhat tentative.

We believe that surgical treatment in a young person should be undertaken if the aneurysm is located in a place where it can be safely approached Ligation of the artery to which the aneurysm is attached is the easiest and most satisfactory operative procedure but it cannot be done unless the collateral circulation to the brain is ample Trapping the aneurysm by placing a ligature on either side of it or any other direct surgical attack is a more difficult and dangerous operation. The mortality rate of saccular aneurysms when untreated except by bed rest [Richardson & Hyland (140), Timberlake & Kubik (164), Wolff and associates (181)], is extremely high, approximately 35 per cent with the first rupture and rising to 60 or 70 per cent if a second rupture occurs during the first period of hospitalization. If the patient recovers after the first rupture of an aneurysm, the chances of survival without serious disability are approximately 50 per cent (Timberlake & Kubik). From the available data it seems fairly certain that the mortality rate in the younger age group of patients has been reduced by ligation of the carotid artery in the neck or, less often, by the other surgical procedures The management of the elderly patient with a ruptured aneurysm raises the most difficult problem of all. Arteriography is poorly tolerated by these patients. Both thorotrast and diodrast injections of the carotid arteries have been attended by transient hemiplegia or aphasia in a rather considerable number of cases, and in a few cases permanent hemiplegia or death have occurred. It must be admitted that in the elderly patient with pre-existing vascular disease, arteriography in any form carries a risk and the same is true of ligation of carotid arteries in neck Very often, even the most gradual methods of arterial occlusion, such as that introduced by Selverstone & White (149), may cause permanent hemiplegia. Also, the mortality in this group of cases without treatment is distressingly high.

Every patient, regardless of age, in whom a diagnosis of saccular an-

the proper treatment, whether medical or surgical, must depend on the balanced judgment of many factors. If surgical treatment is not to be undertaken, arteriography should be avoided in most instances More careful clinical studies of these cases are necessary before a satisfactory program of treatment can be formulated.

The wide use of angiography has created many new problems. As stated above, the procedure is not altogether safe and numerous accidents have been reported such as transient or permanent hemiplegia or other focal neurological signs, and hemorrhage into the sheath of the carotid artery with fatal edema of the glottis. These accidents have been reviewed by Abbott, Gay & Goodall (4), Voris (171), and Dunsmore, Scoville & Whitcomb (48). The effects of intracarotid diodrast on monkeys, cats, and humans has been investigated by Foltz, Thomas & Ward (69). They found that diodrast in the usual concentration had two effects: (*a*) vasoconstriction of the branches of the injected vessel and (*b*) a direct neuronal effect which occurred even after stellate ganglionectomy which prevented vasoconstriction. The vasospasm lasted 60 to 90 sec. and was followed by vasodilatation The enhanced neuronal activity was demonstrable as a seizure pattern in the electroencephalogram Smith and his associates (153) observed no alteration of the permeability of the blood vessels after diodrast arteriography, when tested by the escape of fluorescein from the vessels. Kristiansen & Cammermeyer (103), on the other hand, found that the injected vessels did become permeable to trypan blue but that there were no other gross or microscopic changes.

The effect of carotid ligation, which is the principal surgical method of treatment of aneurysms, has been studied by a number of workers. Sweet & Bennett (161) have shown convincingly that ligation of the carotid artery reduces the intra-arterial pressure immediately above the ligature to a variable degree, and that the reduction is more or less permanent Further, they noted that if the pressure fell to less than 40 per cent of its original value, the patient could not tolerate the procedure in most instances Bakay & Sweet (16) have recently demonstrated that this reduction in the arterial pressure after carotid ligation occurs to the same degree in the branches of the anterior and middle cerebral arteries In other words, the arterial pressure in the cerebral vessels, or in any vascular abnormality situated thereon, may be reduced by carotid ligation Bugnard *et al.* (29) and Bounes *et al* (20) have shown that in humans the ischemic effects of carotid occlusion are easily detected by electroencephalography If the carotid ligation was well tolerated there was no change in the electrical activity; if not, there was delta activity and coma Shenkin and his associates (151) were able to demonstrate a marked increase in cerebrovascular resistance and a reduction in cerebral blood flow in one of four cases developing neurological signs after carotid ligation. Perhaps these several techniques will prove to be useful to the neurosurgeon in deciding whether carotid ligation can be carried out without rendering the patient aphasic and hemiplegic, especially when he is forced

to undertake this operation in the comatose or anesthetized patient. The Matas procedure of compressing the carotid artery for increasing periods of time before ligation has not been dependable.

Vascular malformations.—Since the time of Cushing and Bailey's monograph there has been a radical change in our attitude towards these lesions. This, too, has come about as a consequence of the greater ease of diagnosis by means of arteriography and improvements in surgical technique, particularly the use of the cautery. Whereas Cushing and Bailey believed most of these cases to be quite hopeless from the surgical point of view and recommended x-ray therapy, present-day opinion is that many of these lesions can be excised with relative safety. Probably the most impressive series of cases treated in this way was that reported by Olivecrona and associates (128). These writers demonstrate unequivocally that excellent results can be obtained by total excision of the lesion or ligation of vessels in many cases.

The angioma or hemangioma is a tangled mass of arteries or veins, or dilated vascular channels which cannot be identified even in microscopic sections. The vessels may be small and of uniform size with normal appearing brain tissue between them, in which instance the lesion is called a telangiectasis. Or it may be composed predominately of veins (venous angioma or cavernous angioma), of arteries (arterial angioma) or of both arteries and veins (arterio-venous angiomas) These anomalies may occur in any part of the brain, but often lie in the cerebrum within the territory of the anterior and middle cerebral arteries Another common site is the pons. Usually the angioma is superficial with many ramifications in the pia, and rupture of these abnormal vessels often causes a meningo-cerebral hemorrhage. Sometimes the vascular mass is entirely within the substance of the brain and the hemorrhage therefrom is intracerebral

Cases of angioma come to the attention of the neurologist or neurosurgeon because of the occurrence of repeated subarachnoid hemorrhage, a meningo-cerebral hemorrhage, or the gradual elevation of intracranial pressure resulting from a large mass of abnormal vessels. It should be noted that angioma is more frequent than saccular aneurysm as a cause of subarachnoid hemorrhage in children and young adults Sometimes a recurrent focal seizure of an unexplained stroke is the only manifestation of such a vascular malformation

It is our impression that indications for surgical operation are the development of elevated intracranial pressure and repeated hemorrhage from the angioma Under such circumstances, a surgical procedure is advised unless there is some other medical contraindication The mere demonstration of an angioma that has caused no serious trouble, or at most only a seizure or two, does not justify surgical exploration, for these symptoms can often be controlled by anticonvulsive medication Our tendency in the past has been to err in not always choosing the method of treatment which stands the greatest chance of helping the patient with his clinical problem.

Inflammatory Diseases of Brain Vessels

In recent years several new types of inflammatory diseases of the brain vessels have been brought to our attention. These are difficult to diagnose because the clinical characteristics are not fully known, nor has the pathological anatomy been more than roughly outlined. Limitations in space will permit only passing reference to several of these entities

Carotid artery thrombosis.—Carotid artery thrombosis due to endarteritis obliterans (so-called Buerger's disease of brain arteries) has been reported in more than 200 cases, but probably only 30 or 40 of these stand pathological scrutiny. In many of the other cases the diagnosis of arteritis has been by inference from the clinical data and not by microscopic examination. It is our impression that most of the reported cases are a result of atherosclerosis but that rare examples of an idiopathic arteritis do occur. The literature on this subject has been well summarized by Cooke *et al.* (39) and by Lippmann (114) The common and internal carotid arteries have been affected more often than other brain vessels The pathology of the lesions in the brain arteries has not been worked out in sufficient detail to enable us to state whether it is the same as that in the arteries of the extremities.

Since carotid thrombosis occurs so often in this disease, it should be pointed out that occlusion of this artery is being diagnosed with increasing frequency. Angiography has demonstrated occlusion of this vessel in a number of patients who have had no symptoms of apoplexy or in whom a banal "capsular hemiplegia" or "middle cerebral artery thrombosis" was assumed to have occurred Others with recurrent attacks of hemiparesis, hemianesthesia, aphasia, or monocular blindness [amaurosis fugax, cf. Fisher (60)] have come to our attention Palpation of the carotid arteries in the neck has disclosed a tender, pulseless segment of the artery in some cases Pressure on the globe of the eye on the side of the carotid artery occlusion during ophthalmoscopy will show a reduction in the arterial pressure, i.e. blanching or pulsation of arterioles, which can be measured more accurately by Schiotz tonometer. Manual compression of first one carotid and then the other during electroencephalography will show the vascular insufficiency in dramatic fashion. There is a reduction of consciousness and widespread delta activity over the affected hemisphere when the sound carotid artery is occluded. The procedure is not without risk, for thrombosis has followed vigorous compression of an atherosclerotic artery in a few instances.

The diagnosis of Buerger's disease of the brain vessels should be considered in a young person who uses tobacco, has a stroke and, also, vascular insufficiency of the lower extremities Males are affected more often than females but there has been a relatively high incidence of cerebrovascular involvement in the latter Further details of this clinical picture can be obtained in Lippmann's recent paper.

Temporal or giant cell arteritis—Temporal arteritis, first described by

Horton, Magath & Brown (90), has been the subject of many clinical and pathological reports The inflammatory nature of the disease with damage to the media and adventitia, rupture of internal elastic lamina and giant cell formation, and thrombosis are the characteristic features The clinical picture consists of severe localized headache, tenderness of the scalp, often with palpably thrombosed temporal or occipital arteries, fever, and leucocytosis Several instances of blindness because of involvement of ophthalmic arteries have been recorded. A recent development which has broadened our conception of this class of disease has been the discovery by Gilmour (74) that this same type of disease process may affect all of the major branches of the aorta. Sproule (154), Chasnoff & Vorzimer (33), and Cooke *et al.* (39) have verified the diffuse nature of the disease and published other examples Fortunately, only a small proportion of cases of temporal arteritis have become generalized. The cause and pathogenesis are unknown. Whether or not some of the cases of Buerger's disease or endarteritis obliterans of the carotid arteries are examples of a more chronic stage of temporal arteritis cannot be determined from published reports.

Polyarteritis nodosa—Polyarteritis nodosa has been reported with increasing frequency in the last few years The most recent publication by Kernohan and associates (100) gives a full account of the neurological complications In Kernohan's material, and also in our own, the most frequent neurological disorder is an asymmetrical polyneuritis resulting from periarteritic lesions in peripheral nerves, muscles, and spinal ganglia. Central nervous system involvement, either of the brain or spinal cord, is much less frequent. In those cases with severe renal involvement and hypertension, a hypertensive encephalopathy may occasionally be observed. It has been proposed recently by Zeek, Smith & Weeter (185), Churg & Strauss (34), and Newman & Wolf (127) that there are two different types of polyarteritis nodosa, one in which there is a necrotizing lesion of medium-sized arteries with hemorrhage and thrombosis and extensive involvement of many viscera and peripheral nerves but relative sparing of lungs and brain; and a second form, now referred to as infectious granulomatous arteritis, in which asthma, fever, and eosiniphilia are prominent clinical features, and lung and brain involvement with many granulomatous lesions adjacent to and in the walls of small arteries are frequent. It is suggested that this represents a true hypersensitivity angiitis, in contrast to the first type. The differences between the two must be validated by further pathological cases

The relation of this disease to disseminated lupus erythematosus and to rheumatic fever continues to be discussed Several recent reports of brain artery involvement in rheumatic fever have appeared [Bruetsch (27, 28, Costero (40), Benda (18)]. They state that a primary rheumatic arteritis of brain vessels occurs and is responsible for apoplexy, epilepsy, and even other degenerative syndromes (cf. Benda). Their experience has been so different from that of most pathologists that it is difficult to judge these papers. Many of the lesions show only organized thrombi, and it is impossible to say

whether these were originally embolic or thrombotic. As yet, there is little satisfactory evidence that a primary rheumatic arteritis of brain occurs. There is perhaps a greater likelihood that some of the cases of disseminated lupus erythematosus have an inflammatory disease of the small vessels of the brain We have certainly found occluded vessels in such cases, but usually there has been an associated verrucous endocarditis so that it was impossible to determine the nature of the vascular lesion in the brain. Multiple platelet thrombosis (thrombocytic acroangiothrombosis) which affects brain arteries [Adams, Fitzgerald & Cammermeyer (5)] is another closely related disease.

Thrombosis of cerebral veins and dural sinuses.—Several interesting developments have occurred in this field during the last few years. One has been the introduction of the phlebogram as a means of diagnosing disease of cerebral veins. It was pointed out by a number of the early contributors to the field of arteriography that a delayed x-ray would visualize the cerebral veins and dural sinuses. Within recent years Ray and his associates (139) have introduced another technique, that of either injecting the anterior part of the superior sagittal sinus directly through a burr hole in the skull, or of injecting the sinuses through a catheter that is inserted into the lateral sinus along the jugular vein. Quite satisfactory pictures of the venous system can be obtained in this way. Another discovery of note is that some cases of pseudo-tumor symptoms, i e. headache, papilledema, and elevated intracranial pressure without lateralizing signs, are actually thrombosis of the superior sagittal sinus. It should be pointed out, however, that this does not explain all cases of pseudotumor.

Several more reports of cerebral thrombophlebitis following delivery and after surgical procedures have appeared, and we have observed small numbers of such cases on our wards. This complication tends to occur about the seventh to fourteenth day postpartum or postoperatively at a time when the number of platelets is elevated, the coaguability of blood increased, and the fibrinogen level raised. The prognosis for recovery without disability is good in most of the cases. Cerebral phlebothrombosis of this type is also the most frequent neurological complication of sickle cell anemia and, according to some pathologists, of polycythemia, either the primary form or that which is secondary to lung disease and congenital heart disease.

Conclusion

It can be judged from the volume of the literature on vascular disease of the brain that there is a great deal of activity in this particular field, and that a considerable amount of knowledge has already been accumulated. Much remains to be done before we know the cause and pathogenesis of many of these vascular diseases, and only then will we be in a position to invoke specific methods of treatment. Many of these recent contributions have succeeded in clarifying the problem in such a way that it now becomes possible to proceed with better direction.

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PSYCHIATRY[1]

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Introduction

Psychiatry in 1951 and 1952 moved quietly forward on many fronts. The specialty itself has now become so broad as to have numerous sub-specialties, each concerned with its own research questions No one psychiatrist can any longer be expected to have complete competence in every area of the field, which reaches from genetics, neuropathology, clinical psychology, psychoanalysis, psychosomatic medicine, individual and group psychotherapy, to the psychiatric aspects of hospital administration, rehabilitation, law, industry, college and school educational practices, and psychiatry as it relates to the ministry, to mental hygiene, to preventive services, and to international relations and tensions.

A report on progress which attempted to cover all these fields would be encyclopedic and hence confusing. The major trend, of course, has been in the continuous search for basic causes and for better therapeutic tools Progress in these areas is of necessity slow; no new therapeutic techniques of dramatic importance emerged, but refinements in knowledge took place. If any "movements" can be discerned, it is in the direction of psychiatry's utilization of the skills of other disciplines, particularly the social sciences. Certain pioneering attempts at the development of a true "social psychiatry" are worth describing

Social Psychiatry

This new science is evidenced in the growing number of inter-disciplinary researches into mental illness. Some departments of Psychiatry have added anthropologists and sociologists to their staffs. This coming together of the social sciences and psychiatry stems in part from the social scientist's interest in cultural determinants of personality as well as from the psychiatrist's increasing interest in social, and particularly familial, influences on the numbers and kinds of persons with mental disorders. The phase of the psychiatrist's exclusive concern with the individual, his biography, and the internal dynamics of his functioning seems ready now to broaden into a concern for people in their community context and the social environment which plays such a large role in the formation of character and in the causation of mental disorders

It appears, therefore, that psychiatry has moved historically through a period of almost exclusive concern with the patient in the hospital to the development of interest in the treatment of the ambulatory patient, and now

[1] The survey of literature pertaining to this chapter was completed in September, 1952.

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Introduction

Psychiatry in 1951 and 1952 moved quietly forward on many fronts. The specialty itself has now become so broad as to have numerous sub-specialties, each concerned with its own research questions No one psychiatrist can any longer be expected to have complete competence in every area of the field, which reaches from genetics, neuropathology, clinical psychology, psychoanalysis, psychosomatic medicine, individual and group psychotherapy, to the psychiatric aspects of hospital administration, rehabilitation, law, industry, college and school educational practices, and psychiatry as it relates to the ministry, to mental hygiene, to preventive services, and to international relations and tensions.

A report on progress which attempted to cover all these fields would be encyclopedic and hence confusing. The major trend, of course, has been in the continuous search for basic causes and for better therapeutic tools. Progress in these areas is of necessity slow; no new therapeutic techniques of dramatic importance emerged, but refinements in knowledge took place. If any "movements" can be discerned, it is in the direction of psychiatry's utilization of the skills of other disciplines, particularly the social sciences. Certain pioneering attempts at the development of a true "social psychiatry" are worth describing.

Social Psychiatry

This new science is evidenced in the growing number of inter-disciplinary researches into mental illness. Some departments of Psychiatry have added anthropologists and sociologists to their staffs. This coming together of the social sciences and psychiatry stems in part from the social scientist's interest in cultural determinants of personality as well as from the psychiatrist's increasing interest in social, and particularly familial, influences on the numbers and kinds of persons with mental disorders The phase of the psychiatrist's exclusive concern with the individual, his biography, and the internal dynamics of his functioning seems ready now to broaden into a concern for people in their community context and the social environment which plays such a large role in the formation of character and in the causation of mental disorders.

It appears, therefore, that psychiatry has moved historically through a period of almost exclusive concern with the patient in the hospital to the development of interest in the treatment of the ambulatory patient, and now

[1] The survey of literature pertaining to this chapter was completed in September, 1952.

to the study of the person in the community and society. This should give us increasingly concrete data for preventive psychiatry and public mental health education programs. The working together of social scientists and psychiatrists and the effectiveness of such collaboration for social research is evidenced in the increasing use of the word "interdisciplinary research." The symposia held on this topic at the recent meetings of the American Psychological Association and the American Sociological Association, and the proposed symposium on the same subject at the next meeting of the American Psychiatric Association attest to the growing importance of conjoint research. In September, 1952, the fifth and last of a series of inter-disciplinary conferences was held at Swarthmore, Pennsylvania, just following the American Psychological Association meeting and financed by the United States Public Health Service. In another direction, a year ago the Social Science Research Council set up a Committee on Psychiatry and Social Science Research.

Epidemiological studies of mental illness are to be sure not new. In a volume published in 1950 entitled *Epidemiology of Mental Disorder* (1) there is an extensive bibliography of 362 articles dealing with the subject. The pioneer psychiatric study of this kind in this country dates back to 1935, and was carried out by Roth & Luton (2) in Williamson County, Tennessee. The study attempted to find all the kinds of psychiatric disorders in one county, a fairly typical agricultural community of 25,000 population. The rate of mental health problems encountered of 69.4 per thousand population (in three districts where an intensive house-to-house survey was made the rate was twice as high, 123.7 per thousand) compares closely with the results of the Baltimore survey of 1936 conducted by Lemkau, Tietze & Cooper (3) which was limited to the Eastern Health District, an area of about one square mile in the section surrounding the Johns Hopkins Hospital. This was a residential urban area. The case finding survey was made by searching the written records of all the institutions and agencies dealing with mental health problems, including all varieties of psychiatric disorders. The incidence rate was 60.5 per thousand.

During World War II, data were accumulated by the selective service system and the armed forces indicating that mental illness was the sixth most common disability among all registrants, with a prevalence of 55 8 per thousand. An excellent study was that of Hyde and associates (4) who attempted to analyze the psychiatric problems found among selectees in Boston and their relationship to such various social factors as population density, socio-economic level, educational level, ethnic group, etc. He found a step-like increase in selectee rejections in communities of the best to the worst socio-economic level. There was a high rate of mental deficiency in selectees from the lowest socio-economic group. Psychoneurosis was not related to socio-economic level. The Irish population showed the highest rates for psychopathic personalities and chronic alcoholism.

The classic study in this field, dealing with the ecology of psychosis, is

that of the sociologists Faris & Dunham (5). They studied hospitalized psychotics in Chicago and their incidence in relation to various socio-economic factors. They found that all types of mental disorder tend to show a similar pattern of residence concentration in and around the central business district, with rates declining toward the periphery. Schizophrenia rates characteristically show this pattern while manic-depressive rates show more scatter throughout the city. Persons residing in areas not primarily populated by their own ethnic or national groups show much higher mental illness rates than do the numerically dominant group.

The inter-disciplinary approach to this problem in which the psychiatrist, sociologist, anthropologist, psychologist, and social worker join forces offers much promise for a real solution of the technical research problems involved in community surveys. Within the past two years a number of such projects have been initiated. The Stirling County Project is an intensive study of a county in Nova Scotia It aims to develop case finding techniques, to evolve screening tests applicable to a general population, to map various types of social stresses in the community, and to study the relationships between social stress and incidence and nature of mental illness. At Yale University a similar project is attempting a city-wide survey of New Haven to discover the total number of persons under psychiatric treatment, to analyze the social structure of the area, and to correlate the social variables and the frequency and types of mental illness. In Syracuse, New York, research is under way concerned with the incidence of arteriosclerotic and senile disorders and their relationship to various social and economic factors. In Phoenix, Arizona, the National Institute for Mental Health is conducting a Mental Health Center in which a survey of public attitudes toward mental illness is being carried out on a city-wide basis. Their findings will be of value in comparison with the study made by Elmo Roper in Louisville, Kentucky, reported in *Colliers Magazine* of May 12, 1951 (6) which was concerned with the level of information and attitudes and opinions of individuals in the population toward various kinds of mental disorder. Two other major studies of this kind deserve mention: the Wellesley, Massachusetts, Human Relations Service; and the Yorkville (the northeastern area of Manhattan) Project conducted by the Department of Psychiatry of Cornell University Medical College. Comparable data of course are needed from other areas in order to compare incidence and prevalence findings in rural versus urban areas An extremely interesting set of contrast data is available in the study of Eaton (7), the Hutterite Mental Health Study, of a Hutterite community, a religious sect of closely integrated and communal type of living.

In short, a new discipline of social psychiatry is evolving. Social psychiatry goes far beyond the mere epidemiology of mental illness and comes closer to the study of human ecology, since it is primarily concerned not merely with counting the number of psychiatrically disabled persons in a given community but with attempting the much more basic study of analyz-

ing the influence and impact of social forces and stresses on the formation of personality and causation of emotional and mental disorder.

Psychiatric Education

Psychiatry continued to evaluate its own place in relationship to general medicine and to scrutinize its techniques of education, both in relationship to the medical curriculum and to the training of its own practitioners.

Helped by a grant from the United States Public Health Service, the American Psychiatric Association in conjunction with the Association of American Medical Colleges conducted two outstanding teaching conferences at Cornell University, Ithaca, New York. Deliberations of the first conference of June, 1951, were published in a small volume of 164 pages entitled *Psychiatry and Medical Education* (8) which came off the press in 1952. The volume states in highly succinct manner the deliberations of an outstanding group of educators, deans, internists, psychiatrists, sociologists, etc., concerning the role of psychiatry in the training of medical students, the nature of medical students and their needs, as well as the community's expectations from its practicing physicians, and the administrative frameworks which permit the best utilization of psychiatry in medical college teaching. This volume is strongly recommended to all persons interested in the training of the doctor of tomorrow who needs increasingly to understand patients as functioning human beings living within families and communities which in turn affect health and illness.

The second conference, held in June, 1952, was devoted to the training of the career psychiatrist. During the six days of the conference, major attention was devoted to the subject of ideals and practices in psychiatric residency training. Extensive preliminary reports were prepared by preparatory commissions dealing with such subjects as the history and development of graduate training in psychiatry, the formulation of psychodynamic principles in modern psychiatry; community needs of the psychiatrist; recruitment of candidates for training; training centers and facilities; the role of psychoanalysis in psychiatric training; the role of child psychiatry in psychiatric training, the place of psychiatry in law, industry, the armed forces, and psychosomatic medicine; and the psychiatrist's part in the training of internists, pediatricians, and other physicians. It is expected that a comparable volume of equal importance will appear in 1953 which should spell out for the psychiatric profession where it stands at this time in the training of its own practitioners

Geriatrics

Psychiatry, as other branches of medicine, is beginning to focus increasing attention on the problems of the aging population. This is evidenced in the recent formation of the American Geriatrics Association and in the setting up of a number of psychiatric, medical, and sociological studies of the aging process, such as the one just undertaken by the Department of Pre-

ventive Medicine and Public Health at Cornell University Medical College in connection with the Department of Sociology & Anthropology at Cornell University; an intensive inter-disciplinary study at the University of Texas, and the establishment of a Geriatrics Research Center by the Walt Foundation in connection with Vassar College.

Specific attempts to improve the health of aging people have included the use of testosterone (increased muscular strength, relief of depression, and improved sexual function in aging men are reported), and estrogen therapy for relief of post-menopausal complaints in women (9). Pentylenetetrazole (Metrazol) tablets four times daily for a minimum of 90 days were given to 32 bed-ridden aged patients with arteriosclerosis and mental confusion, with some improvement noted in 26 and marked improvement in 12 (10)

Cytochrome-*c* was reported as ineffective in senile states (11). Severe depressions in patients over the age of eighty have been successfully treated with electro-shock therapy. Luce & Rothschild (12) report correlation between electroencephalographic abnormalities and the degree of mental impairment found in elderly patients In senile psychoses Alpha frequencies of less than 8 per sec and frequent high voltage slow waves were noted.

The psychiatric aspect of geriatric problems is on the increase Vigorous rehabilitation procedures offer hope. The same is true in chronic neurological disorders, hemiplegic patients, etc , as has been amply proven by Rusk at the New York Institute of Physical Medicine Most authors agree that rehabilitation programs must be combined with home care plans and full or sheltered employment.

Alcoholism

Two basic studies have appeared which emphasize nutritional and hormonal aspects in the etiology of alcoholism. Williams (13) proposes a new and radical formulation that alcoholism is a combination of hereditary trait and nutritional deficiency If a diet contains all the necessary nutritional elements, the disease does not appear even in predisposed individuals. Smith's (14) investigation at Bellevue attmepted to relate alcholism to adrenal cortical insufficiency Further studies are needed to prove or disprove both theories Desoxycorticosterone has been reported effective in prompt clearing of delirium tremens and in the reduction of withdrawal symptoms. Similarly, Boswell (15) found prompt and marked relief of withdrawal symptoms from morphine addiction by the use of cortisone.

Diethylthiuram bisulfide (Antabuse) therapy continues to be a useful adjunct in the total psychiatric treatment of alcoholism. It has now been approved by the U. S. Government and is on sale on physician's prescription. A whole series of articles has appeared confirming the value of Antabuse in selected cases where the patient's full cooperation can be obtained. Dangerous reactions occur, and several deaths have been reported Several authors have described psychotic ailments as sequelae The drug is strictly contraindicated in cases with pre-existing brain damage or liver dysfunction.

Other Developments

Genetics.—In the field of heredity and eugenics a number of studies of identical twins point increasingly to the importance of hereditary or constitutional factors in mental disorders, particularly schizophrenia and manic-depressive disorders. The outstanding publications in the field are *Genetics in the Twentieth Century* (16) edited by L. C. Dunn, the proceedings of a *Cold Spring Harbor Symposium on Quantitative Biology* (17); and *Biological Aspects of Mental Health and Disease* (18).

Neuro-physiology and neurology.—Penfield & Flanigin (19) described encouraging results of surgical ablations in patients with convulsions produced by focal temporal lobe lesions. Bailey & Gibbs (20) stated that the psychomotor type of focus originates in the temporal lobe and can be removed by temporal lobe extirpation. There may be independent foci in both temporal lobes. Cossa & Martin (21) produced evidence that the action of insulin on the brain is predominant in the temporal lobe. Chapman *et al.* (22) caused significant elevations both in systolic and diastolic arterial pressure on electrical stimulation of the tip of the temporal lobe in a patient under pentothal anesthesia.

Further studies in multiple sclerosis (23) show that the estimated prevalence ratio for 100,000 population was 42.1 in Winnipeg and 11 8 in New Orleans Mackay (24) concluded that multiple sclerosis is probably more commonly familial than would be explained by chance.

Psychotherapy—Several articles have appeared on the evaluation of psychotherapy. Miles *et al.* (25) conducted a follow-up study on 62 patients with anxiety neurosis 2 to 12 years following psychotherapy in the hospital. Twenty three per cent were found to be markedly improved, 35 per cent were better, and 42 per cent were considered unchanged. A number of factors relate to outcome, such as intelligence, early home situation, and early neurotic traits Patients who were treated by experienced psychiatrists showed only slightly higher rates of improvement than those treated by less experienced physicians.

Psychosomatic medicine.—Binger (26) gives a comprehensive review of the psychogenic influences in essential hypertension. He believes that the psychiatric studies are still inconclusive and will remain so until more is known of the constitutional, physiological, psychological, and pathological elements in this group of diseases. He finds no adequtae proof for the psychogenesis of hypertension. The fact that acute emotional upheaval may result in transitory elevation of the blood pressure should not be used as proof that long-lasting conflict situations act as precipitants to chronic vasomotor constriction. Nonetheless, he believes that psychotherapy offers some patients the best chance for help.

Histamine therapy—The histamine treatment of the psychoses, actively promulgated by Sackler and associates (27), which occasioned considerable newspaper comment, was critically reviewed by the Committee on Therapy

of the American Psychiatric Association (28). The claims were put to retest in three other psychiatric centers where careful controls were utilized. It seems doubtful that histamine is a specific, but is another of the many physiological attacks on schizophrenia which has a certain limited value.

Psychosurgery.—The enthusiasm for psychosurgery continues. Freeman & Watt's book (29) is based upon more than a thousand cases with follow-up of results to more than a decade. It is increasingly evident that good results require proper selection of patients, precise surgery, and the selection of early rather than chronic cases. Transorbital lobotomy has made headway, and Rylander (30) reports that it results in less intellectual downgrading than prefrontal lobotomy. Lobotomy has been extended from the treatment of psychotic disorders and severe psychoneuroses to the treatment of incapacitating psychosomatic disorders with favorable results claimed (31). Friedman *et al.* (32) compared 254 lobotomized patients with one hundred controls, the latter being patients whose relatives had refused permission for the suggested lobotomy. Two years after operation 37 per cent of the operated patients were out of the hospital, not one of the control patients. The first research conference on psychosurgery, whose proceedings were edited by Bigelow (33), deals with criteria for the selection of psychotic patients for psychosurgery. A detailed analysis and comparison of the sexual patterns of 190 contemporary societies which places the Kinsey findings in a broad perspective, since they can now be interpreted in the light of basic social, biological and psychological factors which determine all sexual behavior, was published by Ford & Frank (34)

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DISEASES OF THE RESPIRATORY SYSTEM[1,2]

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The major contribution to the field of diseases of the respiratory system has been in therapy. The introduction of isonicotinic acid hydrazide for the treatment of pulmonary tuberculosis has shown great promise, although the results so far reported perhaps do not bear out the original hopes for this drug and its derivatives. Of continuing interest is the response of allergic conditions affecting the respiratory tract, notably bronchial asthma, to hormone treatment. The response of certain of the pulmonary granulomata in earlier stages has been amply confirmed. There have been further reports of successful treatment of the mycotic lung diseases with antibiotics and chemotherapy. The literature concerned with the treatment of the acute pneumonias has dealt chiefly with the choice of the several effective antibiotics in the bacterial pneumonias and the still open question of the response to therapy in the virus pneumonias. The decrease in the number of papers dealing with chronic pulmonary suppuration, such as lung abscess, empyema, and bronchiectasis, is evidence of the increasingly successful therapy of the acute pulmonary infections. There has been no new approach to the treatment of pulmonary cancer. The emphasis has been centered on early diagnosis and aggressive surgical attack. As in previous years, no attempt will be made to cover all of the literature on these subjects It has been necessary to choose, perhaps arbitrarily, from among numerous contributions of interest, those concerned with specific conditions which are chosen for a more detailed review.

The Acute Pneumonias

Bacterial pneumonias—Flippin & associates (1) treated 93 cases of bacterial pneumonia with four different therapeutic regimes. In the control series of 68 patients, 29 were treated with aureomycin, 22 with chloramphenicol, 17 with oral penicillin. The fourth group of 25 patients in general medical wards was treated with intramuscular penicillin. The end results in all four therapeutic groups were considered satisfactory. The blood levels in the group given oral penicillin were not maintained but the authors suggest that there must have been an ample concentration of penicillin in the tissues to have produced the satisfactory result A report of the Medical Research

[1] The survey of literature pertaining to this chapter was concluded in August, 1952.

[2] The following abbreviations are used in this chapter: BCG (bacillus Calmette-Guerin), ACTH (corticotropin); PAS (p-aminosalicyclic acid).

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Council in Great Britain (2) states that aureomycin, penicillin, and chloramphenicol were all effective in bacterial pneumonias. However, the authors indicate that penicillin is the drug of choice having fewer side reactions. Because of the recently reported cases of toxic effects from chloramphenicol (3, 4, 5) this drug should not be used in acute pneumonias. Now that the longer acting penicillin preparations are available for intramuscular injection, and since it has been amply demonstrated that larger doses of penicillin by mouth are effective, the previous advantages of aureomycin and terramycin no longer hold. This development in change of dosage, and the route of administration make penicillin the drug of choice for the treatment of acute bacterial pneumonia both in the hospital and in the home. There are exceptions to this generalization. Streptomycin, terramycin, and aureomycin, either separately or in combination, are drugs of choice in Friedländer's pneumonia and in tularemic infections as reported by Schwartz (6).

"Q" fever.—Dyer (7), has reported on the clinical aspects of "Q" fever. The disease is more widespread than has been generally recognized. The pulmonary lesions are of a diffuse and patchy infiltration with no specific anatomical characteristics. Laboratory confirmation of the diagnosis of "Q" fever can be made in three ways: by animal innoculation, by complement fixation, or by agglutination tests The author recommends the complement fixation test as the method of choice. Aureomycin appears to have some value in treatment.

Atypical pneumonia.—There is still considerable controversy as to the nature of the so-called "atypical pneumonias." Finkel & Sullivan (8) reported 123 cases with a clinical diagnosis of primary atypical pneumonia seen over a three month period. These authors believe that aureomycin is of definite therapeutic value in treating patients who are acutely ill with primary atypical pneumonia. Temperatures returned to normal in 18 to 60 hr. and the drop in temperature was accompanied by marked symptomatic improvement. The extreme variability of the clinical course of atypical pneumonia makes evaluation of any therapy difficult. Robertson & Morle (9) have made an interesting suggestion that atypical pneumonia is the result of aspiration of mucus or pus from an infected upper respiratory tract. These authors analyze more than 500 cases in military training camps and believe that variability in the radiological features and the clinical course can be explained on segmental aspiration They point out several features to support this theory. The lung involvement is always preceded by an upper respiratory infection, usually a common cold or naso pharyngitis, but sometimes tonsillitis, sinusitis, tracheo-bronchitis or true influenza. Most lesions develop in dependent bronchopulmonary segments or subsegments. In many cases symptoms begin after severe physical exertion during an upper respiratory infection. The high incidence of this type of pneumonia among recent recruits is explained by aspiration of material from the upper respiratory tract during exercise. They further point out that this type of pneumonia usually develops in ambulatory individuals. Antibiotic therapy is recom-

mended only in individuals with evidence of a severe and superimposed infection.

Post pneumonic complications.—Kassowitz & Muscato (10) have reviewed 5927 cases of pneumonia observed among 74,489 admissions to the Milwaukee Children's Hospital over a period of 20 years. The incidence of lobar pneumonia and secondary bronchopneumonia has shown a marked decline since the introduction of chemotherapy and the antibiotics. The over-all incidence of pneumonia has not decreased, probably due to the inclusion of virus pneumonia in recent years. Post-pneumonic empyema decreased from 13.5 per 100 cases in the period from 1929 to 1934 to 1.0 per 100 from 1944 through 1949. The occurrence of bronchiectasis in pulmonary abscess has become decidedly more rare and the mortality from lung abscess has been sharply curtailed. Finke (11) has pointed out that prompt and vigorous treatment of pulmonary infections has not only decreased in incidence of subsequent bronchiectasis but such therapy has also shown that bronchiectasis in its early stages may be reversible. He advises postponement of lung surgery, particularly in children, until it has been demonstrated by a prolonged course of therapy that the bronchial dilatation is permanent. It has become increasingly clear, however, that intensive and prolonged therapy of respiratory infections changes the normal balance among the bacterial flora of the bronchial tree. This is frequently accompanied by a change in the character of the sputum, which becomes less purulent but more mucoid and tenacious. The very effectiveness of such therapy may then bring new complicating factors into the picture.

Shaw (12) points out that mucoid impaction of the bronchi may cause the development of a cystic bronchiectasis and fibroid pneumonitis. Such inspissated material frequently accounts for the persisting x-ray changes long after all signs of the acute infection have disappeared. In such a case of unresolved pneumonia, Muenster, Flance & Sweeney (13) have reported the successful use of streptokinase and streptodornase. Their 75 year old patient was acutely ill, with involvement of the left lower lobe. Three weeks of penicillin therapy failed to produce any noticeable change in the radiographic appearance of the lungs One month after admission, 20,000 units of streptokinase and 9500 units of streptodornase, in a volume of 6 cc. of saline solution, were instilled endobronchially into the several secondary bronchi of the left lower lobe. After 4 hr., the patient began to cough up progressively increasing amounts of thin colorless sputum. A second instillation was carried out on the second day and by the third day there was a striking improvement, both on auscultation and in the appearance of the chest x-ray.

A somewhat similar approach to this problem has been reported using trypsin. Roettig *et al.* (14) using aerosol trypsin in 15 cases reported a decrease in the amount of tenacious sputum. In this same report these authors describe the use of trypsin as a debriding agent within empyema cavities. Seventeen tuberculous cases were treated and while 13 showed positive fluids before treatment, 12 of the 13 became sterile after the use of trypsin

In five nontuberculous cases, four showed complete expansion of the lung following the use of trypsin and a fifth showed improvement but it was necessary to decorticate surgically.

Prolonged treatment of pulmonary infections with antibiotics may alter the bacterial flora to such an extent that superimposed fungus infection may cause serious complications. This has been widely recognized in the colon and in the vagina after prolonged antibiotic therapy. Abbott *et al.* (15) report that a pulmonary aspergillus infection, developing after prolonged antibiotic therapy, caused death of the patient. These authors call attention to the dangers of such prolonged therapy. The general trend during the past year has been to employ smaller doses of aureomycin and terramycin than has been used previously.

Continuation of antibiotic therapy after the acute infection has subsided may actually prevent satisfactory resolution of the pulmonary exudate. Banyai (16) has re-emphasized the value of some of the older methods of evacuating retained secretions. He particularly recommends the inhalation of steam vapor, either with or without volatile oils. In addition he advises the inhalation of a mixture of 5 per cent carbon dioxide and 95 per cent oxygen as a supplementary procedure. Where satisfactory drainage of retained secretions can not be accomplished by these methods, bronchoscopic drainage may be indicated. Such combined measures have greatly decreased the incidence of lung abscess in pulmonary infections. Even where a definite lung abscess has developed, the combination of antibiotic therapy with endobronchial drainage gives excellent results. Byron (17) believes that 80 per cent of acute simple lung abscesses will respond to this treatment. In a smaller percentage of the chronic lung abscesses there is sufficient clinical improvement to permit surgical resection. It is useless, however, to continue such treatment where there is persisting evidence of bronchial obstruction. The possibility of an endobronchial tumor with secondary abscess formation must always be kept in mind.

Pulmonary Tuberculosis

The introduction of isonicotinic acid derivatives for the treatment of tuberculosis has been the most important contribution to this field during the past year. Already a voluminous literature on this subject has been published. Later reports are beginning to emphasize the limitations of these drugs. The use of streptomycin and *p*-aminosalicylic acid is becoming more standardized. With these and all allied drugs, surgical attack on tuberculosis has continued to be vigorous. The use of BCG[2] is still controversial.

Immunity and vaccination.—Myers (18) reviews the long search for immunity in tuberculosis and points out some of the dangerous enthusiasms of the past. He emphasizes some of the dangers associated with mass vaccination with BCG, and insists that tested methods of control should continue to be employed. Continuing reports of the value of BCG vaccination among Indians have been published. Aronson & Aronson (19) report a 15 year follow

up among 1551 vaccinated individuals and 1457 controls. Among the vaccinated individuals, 12 died from tuberculosis, and in the unvaccinated controls, 65 died from tuberculosis. Such figures are impressive. However, the choice of controls in such a relatively small number of cases is always open to question It must be remembered that the enthusiastic reports of mass vaccination from Scandinavian countries in previous years has simultaneously been accompanied by intensive tuberculosis control measures. De-Aberau (20) reported in Rio de Janeiro there was a substantial increase in the tuberculosis mortality rate among infants and young children in spite of extensive use of BCG. During the period from 1945 to 1948 the mortality rate among children from one to two years of age increased 62.5 per cent. In the same period, the tuberculosis death rate for all ages showed a significant decrease, especially in the age group 20 to 40 years. Levine (21) calls attention to the deficiencies in our knowledge of BCG[2] vaccine. He points out the extreme variability in the method of preparing the vaccine and the marked variation in potency from different laboratories Also, the optimal method of vaccination is still open to question.

Schenck (22) points out that much of our present satisfaction in the mortality rate must be tempered by the knowledge that the tuberculosis death rate is not an index of control. He states that of the 9886 active and convalescent cases in the homes of Georgia, 689 were known to have a positive sputum during 1951 In an additional 603 cases, sputum examinations were negative only for six months after having previously been positive.

The decline in tuberculosis has, of itself, brought on new problems. There are now whole sections of the population who are tuberculin negative. The question as to the reaction of such tuberculin negative individuals to subsequent infection is difficult to evaluate. It is well known that among primitive people with no experience of tuberculosis, the disease may assume epidemic proportion Such an epidemic among high school students is reported by Horton *et al.* (23). In this epidemic the first case was discovered in July, 1942 In the succeeding two years, 13 additional cases were discovered making an attack rate of 9.8 per cent for that period. In the authors' words,

> In view of the rural character of the community, with its low mortality rate and scarcity of residents with tuberculosis, many of the inhabitants may never have come in close contact with tuberculosis.... This presumable lack of resistance, more than the factors of exposure and mechanics of transmission, may have been responsible for the explosive and extensive nature of the outbreak.

Actually, we may be creating the background for explosive outbreaks by the very success of the efforts at control. Such reports warrant further consideration of BCG[2] vaccination. The American Trudeau Society recommends and it is endorsed by the United States Public Health Service, that BCG vaccination be used for the following persons if they show negative reaction to the tuberculin tests: (*a*) Doctors, medical students, and nurses exposed to tuberculosis, (*b*) Hospital and laboratory personnel engaged in work with the tubercle bacillus; (*c*) Individuals exposed to infectious tuberculosis in the

home; (*d*) Patients and employees in mental hospitals, prisons and other institutions where the incidence of tuberculosis is high. (*e*) Children and adults, considered to have inferior resistance, if they live in communities with a high tuberculosis rate.

A complicating factor in immunity to tuberculosis has developed through the increasing use of cortisone Traut & Ellman (24) state that the unfavorable effects of corticotropin (ACTH[3]) and cortisone on tuberculosis are multiplying, and record an acute exacerbation of tuberculosis in a 37 year old Negro woman under treatment for rheumatoid arthritis with cortisone. It should be emphasized that all cases of long continued use of these hormones should be carefully followed. *It is wise to screen all individuals for possible* tuberculous infection before instituting therapy.

Drug therapy.—Isonicotinic acid hydrazide has now been given the official name, isoniazid. Among the trade designations for this drug are the names, Nydrazid (E. R. Squibb & Sons); Rimifon (Hoffmann-LaRoche, Inc.); Cotinazin (Pfizer & Co., Inc.) and Pyricidin (Nepera Chemical Co., Inc.); a related compound is the isopropyl derivative, iproniazid, designated Marsilid (Hoffmann-LaRoche, Inc) and Aldinamide (American Cyanamid Co.). This multiplicity of names has caused some confusion. The relationship between chemical structure and antituberculosis activity of a large series of compounds related to isonicotinic acid hydrazide was reported by Bernstein and co-workers (25). The most active compound investigated was isoniazid. Most of the clinical reports concern this particular drug Amithiozone (Tibione), a more distantly related drug, has been reported to be of limited value and there are serious toxic side effects [Childress *et al.* (26)].

The pharmacology of isoniazid and its propyl derivatives has been reported extensively. (27 to 31). In animals, toxic doses produce central nervous system stimulation which comes on as an evidence of acute toxicity and may be prevented by the prophylactic administration of barbiturates as reported by P'An *et al.* (32). Chronic intoxication in animals is manifested by anorexia, fatty degeneration of the liver and subsequent jaundice. From a bacteriological standpoint the reported results in animals are impressive. Uniformly good results have been reported in mice, guinea pigs, rabbits, and monkeys (33 to 39). The drug, in animals, appears to be prophylactic against subsequent infection, as well as effective in established disease. Treatment in mice, when these animals were moribund 14 days after infection showed a high percentage of complete recovery (36).

In the initial reports from the Sea View Hospital, *Bosworth, Wright &* Fielding (40), reporting on extra pulmonary tuberculosis, state that draining sinuses from bone tuberculosis became negative after four weeks in all but one case From the same *hospital, Robitzek, Selikoff & Ornstein (41)* reported 92 cases of bilateral active pulmonary tuberculosis treated with isoniazid and derivatives with encouraging results There was a general increase in appetite and weight with marked decrease in cough and expectoration. Side effects noted were twitching of the extremities, an increase in deep

reflexes, and occasional constipation and dizziness. Urine examinations, blood counts, and liver function tests were performed with no significant changes observed. In a later report, Robitzek & Selikoff (42) report on a change in dosage. In 44 "hopeless" cases of acute progressive tuberculosis, isoniazid and its propyl derivative were given in a dosage of 4 mg. per kg., followed by a still further increase of the isopropyl compound to 10 mg. per kg. In 42 of 44 patients who were febrile, the temperature promptly returned to normal, and the temperature was sustained at a normal level after the tenth day of therapy. The weight gain was the most spectacular finding. The average weight gain was 19.7 pounds in eight weeks Klee (43) reports on 126 cases in whom the dosage given is somewhat larger than that used by the American workers He gave 10 to 15 mg per kg divided into four doses. The usual adult dose was 0.2 gm. doses four times daily. He discontinued the drug for three or four days after the first ten days of treatment, fearing an accumulative effect. In some patients, however, the drug was given without interruption. A decrease in fever and sputum, and gain of weight were noted. Roentgenologically there was regression in 14 of the 61 cases. He states that a 2 per cent solution of the drug may be used intramuscularly without irritation. Such a solution can also be used intrapleurally. An editorial in the *Annals of Internal Medicine*, July, 1952 (44) reviews the recent literature on this subject.

Hinshaw (45) reviewed the antimicrobial therapy of tuberculosis in 1952 and emphasized that treatment with any of the available drugs should be prolonged and continuous He advises concurrent use of streptomycin and *p*-aminosalicylate rather than in sequence in order to avoid bacterial resistance Streptomycin may be given every third day. Surgical extirpation should be deferred until all reversible lesions have responded to medical therapy. The present status of drug therapy for tuberculosis is best summed up by the Committee on Therapy of the American Trudeau Society (46). Treatment is advised in all cases of active disease unless there is some specific contra-indication such as drug allergy, advanced liver, or kidney diseases. As to the choice of drugs, streptomycin or dihydrostreptomycin combined with PAS[3] remains the most effective combination. Streptomycin alone is effective for only 30 to 120 days but a combination of PAS by mouth daily, plus streptomycin two or there times a week, may be given from 18 to 24 months Terramycin and viomycin can not yet be recommended for general use Myomycin is found to be of no value. These authors state that pyrazinamide appears to be effective in animals but in humans the tubercle bacillus becomes rapidly resistant. While admitting that isoniazid and iproniazid appeared to show great promise, for general use these newer drugs should not replace streptomycin and PAS unless it is demonstrated that the organism has become resistant. The best regime available today is a combination of 1 gm. of streptomcyin or dihydrostreptomycin given intramuscularly two or three times each week, plus 12 gm. of PAS given orally each day. If isoniazid or iproniazid are to be used, dosages of 3 to 5 mg. per kg. of body

weight are advised This dosage should be divided and given two or three times each day. The authors emphasize that, while the toxic effects are few, the side reactions should be watched for carefully. These include intractible asthma, prolonged lowering of the arterial pressure and increased susceptibility to the effects of other drugs such as ephedrine, atropine, and meperidine. The value of combined therapy using streptomycin and PAS[2] has been reported by several authors (47, 48, 49).

Surgical treatment.—Extirpation of tuberculous foci has continued to be pursued vigorously. Overholt, Wilson & Gehrig (50) report 426 cases with 437 resections between 1934 and January 1, 1950. In this group, there were 38 postoperative deaths, 49 late deaths, and 302 (70.9 per cent) were considered well. Fourteen cases showed progressive disease The disease was unstable in 21 cases and no follow up was obtained in two instances The over all results have been much better since the introduction of streptomycin.

Corbe *et al.* (51) report on the resection of fibrocaseous nodules (tuberculomata) in a total of 31 cases. There were no serious postoperative complications and no patients had died at the time of the report. Such individuals with this type of lesion are, admittedly, better risks for surgery than cases with cavernous disease Before the streptomycin era there was considerable discussion as to the advisability of removing such lesions. Grenville-Mathers (52) reports on the "natural history" of a group of tuberculomata. In 23 cases under observation three developed cavities with a spread of disease and four developed cavities only In five cases caseous lesions enlarged. Such figures indicate that these solitary lesions cannot be treated expectantly. There is no clinical way to determine which of such lesions are potentially dangerous. Most authors recommend prompt resection. Johansson & Uggla (53) report 54 cases of lobectomy and pneumonectomy in 19 such cases Before 1948, there were seven deaths, six of which occurred in the immediate postoperative period Since 1948, 35 patients have had the operation with only one death.

Kelley & Pecora (54) review 30 patients who had the Monaldi procedure (cavernostomy with drainage). The mortality for the group was 23 per cent and the operation carried a high morbidity They advise follow up of this operation with thoracoplasty or resection. Nissen & Lezius (55) report 16 patients with cavitary tuberculosis where the bronchus draining the lesion was closed surgically. In three individuals Monaldi's drainage had failed. Following this procedure, closure of cavities was demonstrated and there was an immediate decrease in the amount of sputum. In localized disease, the sputum became negative. The procedure is recommended for the treatment of isolated cavities in the upper lobe where previous treatment has failed Amberson (56) has evaluated the development of the surgical treatment of pulmonary tuberculosis from a medical viewpoint. He believes that thoracoplasty and resection offer the best result but emphasizes the proper choice of cases for this procedure.

Pulmonary Cancer

Bronchogenic cancer is statistically increasing faster than any other form of cancer Between 1938 and 1948, annual fatality from bronchogenic carcinoma in the United States rose from 6,000 to 16,000 If the present trend continues, it is predicted that deaths may approach 47,000 annually within 20 years making it the most common form of cancer among men Ochsner *et al* (57) follow the simpler classification and group cancers arising in the bronchi into epidermoid or squamous types and a second group that includes adenocarcinoma, round-cell carcinoma, oat-cell carcinoma, carcinoid, and cylindroma These authors emphasize the statistical association between heavy smoking and the instance of cancer.

The cytologic examination of sputum or bronchial secretion obtained at bronchoscopy, gives diagnostic results in a high percentage of cases. In Ochsner's series, malignancies were found in 60 per cent of 112 cases of proved primary cancer of the lung. Farber and associates (58) examined 6281 specimens of sputum or bronchial secretion from 2066 patients Two hundred forty-one patients had bronchogenic cancer diagnosed by pathologic studies. In these known cases of cancer a previous diagnosis by cytologic means was made in 55 per cent When five or more sputum specimens were examined the accuracy rose to 90 per cent. It is quite generally recognized that bronchoscopy is indicated in suspected cases of lung cancer. It should be emphasized, that where bronchoscopy is not readily available, repeated fresh sputum specimens give almost equally good results.

In spite of all of the emphasis on early diagnosis, the prognosis of pulmonary cancer, as with cancer with any internal organ, is still gloomy. The reported survival after operation is influenced in any series by the number of palliative operations undertaken where no hope of cure can be held out There has been little change in the percentage of survival in more recent reports. About one case in five will survive two years after operation, and where the operation is definitely palliative, only one case in ten may be expected to live two years A statistical analysis of cases seen at the Harlem Hospital has been reported by Gittens & Mihaly (59). All clinics have a large residue in inoperable cases Mayer & Roswit (60) have reported on some of the palliative measures in the management of inoperable bronchogneic cancer. They believe that radiation therapy offers the most benefit, but nitrogen mustard, and neurosurgical procedures have been used.

Woodruff & Nahas (61) have reported an interesting observation. In a series of 23 cases of bronchogenic carcinoma there were 12 of squamous cell type sufficiently differentiated to form epithelial pearls All 12 of these tumors were situated in the upper lobes, in all but one there was a large calcified focus in the same lobe or in the adjacent lymph nodes Only two cases showed evidence of active tuberculosis. They suggest the possibility that previous bronchiectasis in this region may have favored the development of cancer This observation is particularly interesting in the light of speculation

as to the effect of heavy smoking on the development of cancer of the bronchus. The percentage of individuals developing bronchogenic cancer who are also heavy smokers is undeniably impressive and probably causal Conversely, the percentage of heavy smokers who develop bronchogenic cancer is statistically *insignificant. There must be some predisposing condition.* The authors' suggestion that pre-existing bronchiectasis may be a factor seems reasonable.

Bronchial Asthma

Since the introduction of cortisone and corticotropin for the treatment of bronchial asthma, numerous confirmatory reports have been published confirming the effectiveness of this treatment. Schwartz (62) has reported on orally administered cortisone in intractible bronchial asthma He gave 31 courses of treatment to 22 patients. In 26 instances, symptoms were relieved. Five courses in five different patients had no beneficial effects. Four of the five failures were in patients with emphysema Relief was much greater than that obtained previously with any other medication. Relief with *orally administered cortisone occurred 5 to 72 hr after the onset of therapy.* On adequate dosage, relief was maintained during cortisone administration The symptoms of 18 patients (61 per cent) recurred within two weeks after cortisone was discontinued. There was no relationship in this series between *the total dosage or the duration of therapy and the length of* remissions. Ankle edema occurred in one patient, an initial decrease in urinary output in four, an additional gain in weight in six Occasional glycosuria disappeared on decreased dosage of cortisone. One patient died from an acute asthmatic attack. The autopsy findings showed no evidence of relationship between cortisone therapy and the cause of death The initial daily dosage of cortisone ranged from 200 mg. to 300 mg for adults; the daily dose for the second day ranged from 100 mg to 200 mg. and was followed by 100 mg daily until adequate relief was obtained When relief occurred, the dose was reduced to the minimum amount necessary to obtain adequate relief. The total daily dose was given orally in four equal doses at 4 hr. intervals. The dose for children was 25 to 75 per cent of the adult dose. In adults the average maintenance dose was 25 mg. twice daily, although an attempt was made to adjust the dose to the clinical response of the patient. The duration of therapy ranged from 1 to 45 days

Segal & Herschfus (63) have reported on the intravenous use of ACTH[2] for bronchial asthma. This hormone has been found by previous observers to be more effective intravenously than by subcutaneous administration. The authors employed a continuous infusion of 5 per cent glucose in distilled water; the rate of flow was 30 drops per min , or 3 l. in 24 hr. In most cases, 0.5 mg. of aminophylline was given additionally to each liter; 10 mg. of ACTH were added. Subsequently, depending on the results, the hormone

treatment. In ten cases of acute or intractible bronchial asthma, 11 intravenous courses were given. Symptoms were partly or completely relieved in all instances, then recurred to some extent. During subsequent observation, however, only two subjects had serious relapses.

The cases of true bronchial asthma should be differentiated from those cases of asthmatic bronchitis associated with emphysema. In these individuals, the symptoms are more continuous and the difficulty in breathing is not of the spasmodic nature. Beale, Fowler & Comroe (64) report pulmonary studies of asthmatic patients in an attempt to differentiate among the various types of dysfunction. During asymptomatic periods the pulmonary function of most asthmatic patients in all groups is abnormal. Such persons usually have decreased vital and inspiratory capacities with increased functional respiratory capacity and residual volume both absolutely and in relation to total capacity. The maximum breathing capacity is lessened. They state that pulmonary function tests offer the means of identifying those patients whose lungs are abnormal between attacks and provide an objective measure of the reversibility of changes with therapeutic procedures. A sharp differentiation between pulmonary emphysema and chronic obstructive disease is difficult to make on the basis of ordinary pulmonary function tests. With pure uncomplicated bronchial asthma, the pulmonary function is diminished, because of obstruction to the flow of air which results in hyperinflation of the lungs at the resting respiratory phase. In pure emphysema, the reduction in the elasticity of the lung is responsible for poor pulmonary function. Bronchial obstruction in chronic asthma may be due to constriction of bronchiolar smooth muscle, to mucosal edema, congestion, or secretions. Therefore, more persistent and varied therapy should be carried out in order to increase lung function. This should include the use of agents to control infection (administered systemically and by aerosolization) bronchodilators, and adrenal cortical hormones.

Lukas (65) reports as a complication of ACTH[2] therapy, bronchiolar obstruction, thought to be edema due to the drug. He studied pulmonary function in nine patients, before and during administration of the hormone These individuals had various types of chronic lung diseases, characterized by evidence of emphysema Subjective and objective improvement, sometimes dramatic, occurred in those patients whose disease was secondary to or complicated by bronchiolar obstruction, and was minimal or absent in those patients without obstruction. This observation, together with the pattern of change in pulmonary function, suggested that ACTH and cortisone exerted a sustained broncho-dilating action. The effect of these agents on the bronchial tree was greater than the action of conventional bronchodilators in at least two patients with chronic obstructive emphysema.

Miscellaneous Conditions

Beryllium poisoning—Van Ordstrand (66) and Dutra (67) have reviewed this subject. Since the first death of a worker in the beryllium industry in

1940, Van Ordstrand has had the opportunity to observe many phases of poisoning in more than 450 cases. In acute respiratory poisoning from beryllium, pneumonitis begins with a nonproductive cough and progressive dyspnea followed in two or three weeks by demonstrable roentgen lesions An edematous mononuclear exudate forms within the alveoli, producing symmetric infiltration. Approximately one of eight patients dies of asphyxia, with or without cor pulmonale, about four weeks after onset. The features of chronic lung changes are now well established. Roentgen shadows may precede symptoms, which appear up to 10 years after exposure. Cough, shortness of breath, anorexia, and weight loss develop less rapidly than in acute cases Lesions are interstitial, granulomatous, and evident as fine disseminated nodular infiltration. Although no actual antidote has been found, ACTH[3] and cortisone frequently relieve symptoms and reverse granulomatous conditions.

Pulmonary sarcoidosis.—Small (68), among others, has reported roentgenographic improvement after administering cortisone by mouth. A dosage of 100 mg. daily was given from four to six weeks in four cases of pulmonary sarcoidosis. Disappearance of cough, expectoration, and dyspnea was rapid. Pulmonary function tests showed good recovery of vital capacity, breathing capacity, and ventilatory reserve. Beneficial effects of cortisone result from inhibition of connective and granulomatous tissue growth.

The use of ACTH and cortisone in allergic conditions has been reviewed by Evans & Rackemann (69), and the particular use of these hormones in diseases of the chest has been reported in a symposium (70). The consensus of the symposium may be quoted in some detail

Summary: . . . a new state in the study and treatment of disease is the field of attempting to change the reaction of the body to a disease process rather than the attempt to attack the disease itself.

As regards the two new substances in question, it must be remembered that, although their effect as measured by end results may be much the same, they are different and the mode of action is different.

ACTH is a polypeptide liberated by the anterior lobe of the pituitary gland, which acts on the cortex of the adrenal gland to cause production or liberation of steroid hormones

Cortisone is a steroid hormone itself which has its origin in the adrenal cortex and acts on the periphery of the body.

ACTH requires an intact adrenal cortex if it is to be effective, whereas cortisone is a substitution product and thus does not require an intact adrenal. Cortisone for all practical purposes produces similar results to those created by stimulation of the adrenal gland by ACTH.

In the use of these drugs there are many and profound changes occurring in the

cumulation. Likewise, blood pressure should be checked and a baseline of blood sugar and eosinophil counts should be made. In general, sodium intake should be limited, the protein intake increased, and supplemental potassium should be given.

As regards clinical use, to date it has been found most effective in asthma, Loeffler's syndrome, and possible Böeck's sarcoid. Whether there is any application to tuberculosis is yet to be determined. Thus far the evidence points to a deleterious effect on the disease while the patient feels improved. There is some suggestion that methods of its utilization may be found and the substances applied to emphysema, pulmonary fibrosis, and interstitial pneumonitis. In bronchogenic carcinoma, although the disease, as such, is not involved and its course remains unchanged, the condition of the patient may be sufficiently improved to justify its use.

Certain dangers must be borne in mind First, the development of severe diabetes in individuals who might be considered prediabetic. Second, the chance of infection developing and getting entirely out of hand before it is recognized, and third, that allergic phenomena may be caused by ACTH as well as relieved by it.

The dosage will vary with the individual and the type of case treated, it being a good rule to use the lowest dosage that will produce the adequate results. There is some difference of opinion as to whether long term continuous therapy is more desirable than repeated courses of more intensive treatment.

Mycotic disease—In actinomycosis, penicillin and sulfadiazine have been the drugs of choice, although streptomycin, bacitracin, and aureomycin are reported as useful. The observation that stilbamidine (4,4'-stilbenedicarboxamidine) was a useful therapeutic agent for infections caused by *Blastomyces dermatitidis* led Miller, Long and Schoenbach (71) to use this drug in a case of actinomycosis resistant to prolonged administration of penicillin and sulfadiazine. The lesion was in the neck, and apparently complete recovery took place. Although this was not a pulmonary mycotic lesion, this report suggests that stilbamidine may be tried in mycotic lesions not responding to other therapy.

Pneumoconiosis—A case of talc pneumoconiosis has been reported by Friedman, Bell, & Solis-Cohen (72). Free silica is the common cause of pulmonary fibrosis in industry Talc, a hydrous magnesium silicate, is an unusual cause for such pneumoconiosis. The reported case had typical clinical and roentgen characteristics The patient, a 65 year old white man, had worked for 24 years handling rubber thread coated with talc powder. This report deserves widespread attention as it has been commonly thought before that only the long fiber silicates, such as occur in asbestos, were responsible for pulmonary fibrosis. Apparently exposure to the silicates must take place over a long period of time to cause pulmonary fibrosis

Fibrosis of industrial origin should be sharply differentiated from those fibroses which develop in older individuals along with emphysema. Rubin *et al.* (73) have reported a case of diffuse interstitial fibrosis of the type first reported by Hamman & Rich in 1944. They have reviewed 13 additional cases found in literature Since the exact diagnosis can be made only by autopsy, the authors suggest that the condition may be much more prevalent

than is recognized, and that recovery may take place. The etiology is unknown but it may be a tissue response to virus infection.

In recent years, x-ray evidence of a nondescript pulmonary infiltration has focused attention on Loeffler's syndrome, tropical eosinophilia and related conditions. Reeder & Goodrich (74) have reported eight cases of pulmonary infiltration with eosinophilia, illustrating reversible, prolonged, and fatal outcome in this condition. The clinical picture and symptomatology vary. Over 25 per cent of Loeffler's original cases were detected during routine chest x-ray examination. However, dyspnea and severe wheezing may occur. Physical findings are often absent. Occasionally, impaired percussion and diminished breathe sounds are found. The eosinophil count in peripheral blood may reach 80 per cent. The eight cases reported by these authors is a group distinct from tropical eosinophilia. The results from hormone therapy in this group of cases is moderately encouraging. A progressing periarteritis nodosa accompanied the syndrome in one case, confirmed by postmortem examination. During life, the diagnosis of periartheritis nodosa must be considered in all such cases and muscle biopsy performed where indicated. Crofton *et al.* (75) report 16 cases of pulmonary infiltration with eosinophilia and review 450 cases collected from the literature. Many of the cases occur in individuals with a strong allergic background. The authors suggest that the condition is probably a "disease of adaptation." They suggest that it is a reaction of the body to a variety of stimuli. Those cases where there is bronchial infestation with mites should be classified as tropical eosinophilia In cases with gross lesions of the blood vessels, the condition is probably periarteritis nodosa. For simple cases they prefer to use the term "Loeffler's syndrome."

Pressure breathing in chest disease.—Barach, Eastlake & Beck (76) have published a clinical follow up of results of therapy using the immobilizing chamber. The results are moderately encouraging. Motley & Tomashefski (77) have used pressure therapy with a mask and oxygen. Twenty minute treatments three times a day, were combined with the use of bronchodilators and other collateral measures so that evaluation of the actual results of this pressure therapy is difficult. The usefulness of these procedures appears to be limited

Pneumothorax and hemopneumothorax—Beatty & Frelick (78) have reviewed the literature on the subject of treatment of hemopneumothorax and have reported seven cases. These authors are in general agreement with the war experience that prompt aspiration of both blood and air should be carried out. They advise early thoracotomy in cases of uncontrolled bleeding. Streptokinase and streptodornase are recommended for use to remove residual clots and fibrin. Surgical decortication is advised if the lung fails to reexpand because of an organizing clot. In pneumothorax uncomplicated by bleeding, Kreutzer, Brizzolara & Rogers (79) advised continuous intrapleural suction It is hard to see why cases of pneumothorax without bleeding

should be aspirated cautiously. Davenport (80) has recommended prompt and vigorous aspiration in cases of spontaneous pneumothorax. Re-expansion of the lung does not favor further leakage of air and failures have been only in those cases where the lung could not be re-expanded promptly. These observations, as well as reported results of prompt aspiration in hemonpeumothorax suggest that, with or without complicating bleeding, prompt re-expansion of the lung is the goal of treatment

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PHYSICAL AGENTS AND TRAUMA[1]

BURNS AND FREEZING

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Physical agents and trauma continue to exact an ever increasing toll on humanity. The whole subject is such an important one and the literature is so vast that for the purposes of the present review it was thought best to limit the discussion to Burns and Freezing. Recent advances or recent consolidation of past advances has made such a review a timely one and the current military action in Korea has made it an urgent one. Even under the headings of Burns and Freezing, not all aspects can be covered without detracting from emphasis on more pertinent subjects.

BURNS

The subject of burns is an important one for the national economy even in peace time. In the United States during the past 50 years, an average of over 5000 deaths *per annum* from burns, exclusive of conflagration, has occurred. With military action in existence and with atomic and hydrogen bomb disasters potentially in the future, this subject becomes of even greater significance and is one that should receive more emphasis than it has. Speaking of burns themselves, Moore (69) makes the terse comment concerning estimation of the depth of a burn: "It is deeper than you think."

The treatment of burns has advanced markedly in the past 27 years since Davidson (29) introduced the tannic acid method. While the tannic acid mode of therapy has been abandoned during the last half of this quarter of a century, it served a very useful purpose in focusing attention on the entire subject of burns Advances made, particularly in the last 15 years, and partially stimulated by World War II, provided not only the introduction of the occlusive dressing method of treatment by Allen and associates (4 to 7) in 1941, but also developments in the treatment of burn shock, emphasis on early skin grafting, and developments of better methods of skin grafting. The tannic acid method of local treatment was preëminent between 1925 and 1941 During World War II and up until 1948 the occlusive dressing method was the undisputed leader in the major clinics in this country, but in 1948 its supremacy was challenged by a revival of an old treatment, the open air method.

The exposure or open air method of burn treatment is undoubtedly the oldest of all burn treatments. It was discussed in the book, "The Treatment of Burns" by Harkins (46) in 1942 with condemnation at that time. Sneve (96) in 1905 was an advocate of the exposure method. The method fell into disuse and

[1] This review covers the period from approximately January, 1951 to November 1952.

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fever in as many, if not more, cases than following the occlusive dressing method, prolonged hyperpyrexia lasting for weeks is frequent in the latter method of treatment and is nil in his experience in the exposure cases Wallace (103, 104) reiterated that exposure to dry heat was a factor in the abandonment of the early attempts by Sneve and others of the exposure method. This Scottish author discussed further the role of temperature in deciding which method of local burn treatment to use, as follows:

> In warm dry climates I consider drying by exposure to be the ideal method; in warm moist climates it should be tried because even absorptive dressings are not satisfactory; during the cold seasons of temperate climates absorptive dressings should be used until the patients can be admitted to a warmed room.

Pulaski and co-workers (83) made an additional report concerning their experience with the exposure or open air treatment of burns. Partial-thickness burns up to 30 per cent of body surface and involving predominantly one side of the body are particularly suited for treatment by exposure, as are burns of the head and buttocks If the regimen as outlined is adhered to, such burns heal with a minimum of discomfort to the patient and minimal nursing assistance

Blocker *et al.* (18) stated that from their experience they believe the conversion of the burned tissue into a dry slough to form a mechanical barrier against invasion by pathogenic organisms, which require warmth and moisture for growth, is based on sound physiologic principles. In another paper Blocker (16) stated that he believes that open-air therapy is the only practical method yet devised of coping with large-scale burn disasters during the emergency period before reconstructive centers can be set up. In an additional paper this author stated (17) that he has found the exposure method "a most satisfactory technique for treating acute burns, both mild and severe"

McDowell (63) discussed the advantages, but also cited some of the disadvantages, of the exposure method He noted that bed confinement and special traction apparatus were found to be almost routinely necessary in order to really maintain the important advantages Repeated motion, especially on flexor surfaces, will usually cause breaking of the eschar within two or three days, and prolonged or recurrent contact with bedclothing, supporting apparatus, or any material will result in frank disintegration of the eschar in about the same time. Wherever the eschar is broken, surface infection, exudation, formation of exposed granulation tissue, and further loss of eschar may ensue He concluded this portion of his analysis with the following pithy statement: "To casual observation the method may appear to be one of detrimental neglect and with casual employment it may become just that." Evans (39) discussed the open method and made the following observations· In deep burns, separation of burn slough is much more rapid when the closed method is used The chief advantage with the closed method is for encircling burns of the limbs or trunk. With these it is exceedingly diffi-

was revived by Wallace (102) of Edinburgh, Scotland in 1949. It should be pointed out at this time that Wallace's revival had one important difference from the technique as used by some of the previous authors, namely, that the previous authors used not only exposure, but also heat. Wallace used the exposure at room temperature In other words, the previous authors had not only used drying, but also a temperature which would be ideal for bacterial growth in the wound. Wallace used only the drying effect of exposure to the air.

Colonel Pulaski (12) of the United States Army visited Wallace's clinic, returned to the United States, and introduced the method into Brooke Army Hospital in Texas. Blocker (16), head of the department of Plastic Surgery at the University of Texas in nearby Galveston, took up the method and subjected it to further scientific appraisal.

Early Local Treatment

The present status of the exposure method—In a brochure appearing in 1952, Artz *et al.* (12) outlined their experiences with the exposure treatment of burns as observed at Brooke Army Hospital, Fort Sam Houston, Texas. These authors concluded that the treatment of burns by exposure to air is an effective and practical method of local care. Its successful application depends on the development of hard crusts formed chiefly from the exudate of partial thickness burns, and on the integrity of dry eschars composed of the dead skin of deep burns This work, initiated by Colonel Edwin J. Pulaski, is outstanding in developing this mode of burn therapy in this country. Pulaski, speaking at the Symposium on Burns of the National Research Council (82), gave the following advantages of the exposure method of treatment:

(*a*) Time consumption of application and expense of pressure dressing are eliminated. (*b*) Marginal skin surrounding the burn does not become inflamed, soggy, or macerated, (*c*) Odor is absent; (*d*) Pyrexia is of relatively short duration; (*e*) The incidence of clinical infection is gratifyingly low; (*f*) Appetite and feeling of well being return rapidly; (*g*) After the coagulum is formed, nursing care is reduced to a minimum, and many patients become ambulatory; (*h*) Because infection is reduced, healing time is shortened and the hospital stay of the patient is lessened; (*i*) Finally, there is less need for grafting.

On the negative side, Pulaski points out that the method of treatment has certain disadvantages It is definitely a hospital procedure and should not be carried out on ambulatory patients Furthermore, circumferential burns are exceedingly difficult to treat by this method. Finally, patients, visitors, attendants, or even physicians may yield to curiosity and peel off some of the crust to peek beneath it. The possibility of picking at the crust is a definite objection to the method, particularly with patients that are over-curious or undisciplined Speaking at the same symposium, Wallace pointed out that, whereas the exposure method of treatment is followed by early and mild

group of leading clinics in this country but is unpopular with the majority of men who treat burns The unfavorable British view is epitomized by the statement of Colebrook (25) who states as follows·

> Some American surgeons believe that, in spite of the haemoconcentration, it is desirable to give blood instead of plasma or a substitute because of the red blood-cells known to be destroyed in severely burnt patients, and all agree that a considerable degree of anaemia often develops within a few days of the injury. To us in Birmingham it has seemed unreasonable to add more red cells when the proportion of these in the patient's blood is already too high; but in very extensive burns we add an occasional bottle of blood after the haemoconcentration has been corrected or prevented if the patient's clinical condition is satisfactory. And, of course, we use blood-transfusions freely for the anaemia that develops a little later; and also to compensate for the loss of blood during grafting operations.

The Swedish view is expressed by Gelin (44), who stated as follows: "We do not give transfusions of whole blood in the acute stage unless there is anemia. Haemoconcentration must be regarded as a contraindication to transfusions of whole blood."

Quinby & Cope (84) studied the blood viscosity and its relationship to whole blood therapy of burns in patients and in dogs. Their studies indicate that while whole blood augments the high hematocrit and therefore increases the viscosity, no maltoward effects of these two changes could be demonstrated in their patients or experiments In a discussion of Quinby & Cope's paper, Abbott (1) spoke in favor of the use of whole blood in the acute treatment of burns. Evans and co-worker, (42), likewise, spoke on the affirmative side, as follows·

> When the burn is 35 per cent or more of the body surface we have found it advantageous to give whole blood in approximately 2 parts to 1 of plasma or whole blood alone Whole blood may be administered in the presence of continued hemoconcentration. Whole blood remains the bulwark of our plan of intravenous therapy for the treatment of shock in the extensively burned patient

McCarthy (62), in experiments on rats, found that whole blood in combination with plasma gave a much higher survival rate in burned animals than any other treatment that he used For example, whole blood and plasma gave a percentage of 75 per cent survival, whereas the recovery rate with plasma alone was only 17 per cent; gelatin, 17 per cent; and polyvinylpyrrolidone, 33 per cent. Of all the agents other than the whole blood plasma combination in McCarthy's experiments, saline-lactate gave the best results (42 per cent). McCarthy did not compare directly the effects of whole blood alone with plasma alone, but since most authors who use whole blood use it in conjunction with some plasma, his combination treatment is essentially advocated by most of those who utilize whole blood Moyer (74), in a discussion of McCarthy's paper, also spoke in favor of whole blood.

Millican *et al* (67) and Millican, Tabor, & Rosenthal (66), described the acute hemodynamic effects of therapy with various intravenous solutions in

cult to get a dry wound with the exposure method. In his experience, it proved difficult to immobilize the burned part properly when the exposure method is used The exposure method appears to be more useful for burns of the face and perineum. In his experience, the exposure method has given very poor results when used for the burned hand. Hyperpyrexia, which is fatal unless effective cooling measures are rigorously employed, is more often encountered when the closed method is used, especially if the burns are extensive (50 per cent or more), and involve the limbs and trunk. A high relative humidity and a low environmental temperature are probably limiting factors for the successful use of the exposure method.

Before leaving the subject of the local treatment of burns, a few other papers not directly concerned with the exposure method should be considered. Allen (5) and Allen & Bell (6) discussed their recent results with the occlusive dressing method of treatment based on an experience with 1000 hospital patients. These authors pointed out that the method is useful in cases that are to be transported. Large pads measuring either 22 in.×12 in. for small parts of the body, or 40 in.×24 in. for the trunk or lower extremities, when prepared in advance, might be a useful way of preparing for potential atomic bomb disasters. Choy & Wendt (24) discussed the use of an occlusive spray which was tested on hogs following burns This spray is the plastic XC7-9C, which is a chemically inert vinyl resin. The properties of its solvent, ethyl acetate, are well known. In air concentrations lower than 400 p.p.m., it is nontoxic; above this level, it can produce headache and mild narcosis if inhaled, and irritation to conjunctiva, gums, and respiratory passages by contact. Chronic poisoning leads to secondary anemia, leukocytosis, cloudy swelling, and degeneration of viscera. This reviewer, however, would like to point out that there are species differences and some permanent effects which may not show up immediately. The history of the treatment of burns by the application of various drugs to extensive burned surfaces indicates that physicians have never properly considered the potentialities of surface absorption of these drugs. It took approximately 15 years before suspicion was directed at tannic acid in this regard, and before its final abandonment because of the strong possibilities of liver necrosis as a direct result of absorption of the tannic acid. The same may apply to the method of Choy & Wendt, although it is only fair to point out that they have made toxicological studies on their preparations.

Early General Treatment

Administration of fluids for intravenous supportive therapy—Whereas the early local treatment of burns has been simplified in recent years and only the exposure method and the occlusive method are under debate in the bulk of the literature, the fluid therapy of burns is in a state of confusion. Four types of fluids are under discussion. These are whole blood, plasma, saline, and plasma substitutes such as gelatine, macrodex, and dextran.

The use of whole blood in the treatment of burns is popular with a small

Thorsen (91) described the use of macrodex (or dextran Ph, as it was first called). They concluded, on the basis of treatment of 11 patients, that macrodex seems to be as good as plasma for the treatment of shock from burns. Gelin (44) also found macrodex to be excellent for maintaining osmotic pressure in the circulating blood following burns, and in combination with an oxygen tent it was an effective method of therapy of burn shock. Millican, Stohlman, & Mowry (65) presented a warning concerning the use of dextran, polyvinylpyrrolidone and oxypolygelatin, because they found in experimental animals that had been burned, toxic reactions following the use of certain of these agents which were not apparent when the agents were used on normal animals

Value of ACTH and cortisone in general supportive therapy—Attempts to assay the efficacy of ACTH and of cortisone in the treatment of severely burned patients are a natural outcome of the introduction of these two new drugs. Crassweller *et al* (28) reported three cases of severe burns treated with cortisone. One of these patients died with a normal histologic distribution of lipoid material in the adrenal cortices at necropsy. The second patient died on the twenty-fourth day, apparently from sepsis, and the adrenal glands showed a decrease in sudanophilic material The third patient did well and the authors postulated that the recovery of the patient might have been a result of the administration of cortisone.

In this country, the report of Whitelaw (108) aroused a great deal of interest. This author reported a patient, aged 23, who was burned with a resultant increase in hematocrit to a level of approximately 46 as a maximum After a thorough case study, this author stated that the case demonstrated the potentially tremendous saving in both medical personnel and supplies as compared with conventional methods of therapy. The enthusiastic report of Whitelaw was not accepted by all authors. However, a number of writers did report favorable results in very small series of cases. Adams and associates (2) reported three cases of children treated with ACTH. These authors believed that improvement followed the administration of the drug Day & Babalis (30) also reported a case with favorable results Trumper (99) stated that research in ACTH and cortisone therapy "has yielded sufficient evidence to justify the use of these hormones in deep and external burns with the confident expectation that they will cause diminution of inflammation, pain, and perhaps shock."

This reviewer, however, is of the opinion that application of ACTH and cortisone to the treatment of burns rests on a very uncertain foundation, and is opposed to its routine use Evans (40) stated in this regard: "The enthusiastic use of ACTH in the early treatment of the burn patient has not been substantiated " Moore (69) has the following comments to make about the use of ACTH in burns: "There is no evidence that ACTH stimulates further the adrenals of the burned patient, already stimulated endogenously, in the ordinary case when blood pressure is easily maintained, there is no indication for cortisone."

the treatment of burns, as well as a comparison of the survival rate following therapy. These authors found no difference between whole blood and plasma upon the survival from burn shock when either single or multiple doses were given. Approximately 50 per cent greater amounts of saline were required to equal the effects of plasma under these conditions.

In consideration of the use of saline as a method for treatment of burn shock, various formulas have been devised for the administration of fluids. Shapiro (93) discussed such a formula for the administration of plasma. Richards (88) discussed the use of oral and intravenous saline. He stated that oral saline is especially useful in burns of moderate severity or extent Kyle & Wallace (54) presented a fluid replacement formula for burns exceeding 30 per cent of the body area as shown in Table I. Moore (69) used the following rules for early fluid replacement in burns: (*a*) Burns over 25 per cent

TABLE I

FLUID REPLACEMENT FORMULA FOR BURNS EXCEEDING 30 PER CENT OF BODY AREA
(Kyle & Wallace (54))

Calculate 10 per cent of body weight.
Fluid requirement for 48 hr. = 10 per cent of body weight plus twice daily metabolic fluid requirement.

First 24 hr.	$\frac{3}{4}$	8 hours 16 hours	$\frac{1}{2}$ $\frac{1}{4}$
Second 24 hr.	$\frac{1}{4}$	24 hours	$\frac{1}{4}$

body surface; 10 per cent body weight plasma in first 48 hr. (*b*) In addition, lung, skin, and urine losses must be replaced, the latter two with saline; (*c*) Of this total ration, about one-half should be given in the first 12 hr , the rest more slowly. The intravenous route is preferred; (*d*) One whole blood transfusion of 500 cc in the first 48 hr.

Prendergast, Fenichel & Daly (81) presented the first known electrophoretic studies of a series of human burned patients which demonstrate that the gamma-globulin concentration appears to provide a good index of burn severity In major burns, there is a great increase in gamma-globulin concentration. These Detroit authors pointed out that electrophoretic instruments show that whole-blood transfusions, even when frequently repeated, do not correct the abnormal blood picture produced in moderate to serious burns They stated.

> Evidence available at this time suggests that better therapeutic results might be secured if, in addition to whole blood, burn patients requiring blood replacement therapy were to be transfused with purified normal human serum albumin or a blood substitute suitable for albumin replacement.

The use of plasma volume expanders or plasma substitutes in the treatment of extensive burns has received a continuing interest. Rosenqvist &

to be a life-saving measure when used as a temporary covering to the burned area When the use of cortisone and ACTH became popular, the theory was postulated that these drugs might block the antigen-antibody response of the skin and so make homograft transplants possible. Whitelaw (108) reported that this was indeed the case with 40 homologous pinch grafts applied to one patient Since homologous grafts have been known to survive up to even a year without these drugs, and since this article was published less than a year after the patient received the original burn, the possibility still exists that Whitelaw's grafts were only a temporary take, Day & Babalis (30) believed that the use of ACTH was beneficial in making their autogenous grafts more successful.

There has been a great deal of recent interest in skin grafts from various aspects Mir y Mir (68) has written an excellent article concerning the biology of the skin graft. Rogers (89, 90) has written two excellent reviews concerning skin homografts. General comments concerning experimental aspects include those of Stark (97) relating to the lymphocytic response after homoplastic skin grafts, Weisman & Cannon (106) concerning the failure of heat treatment to prolong the survival of skin homografts in guinea pigs; the results of Glover (45) on experimental cutaneous grafts to litter mate animals which were successful early in life, although in later life similar grafts between the same animals failed, the studies of Allgower, Pomerat & Blocker (10) concerning the influence of serum and of wound healing agents on human epidermis *in vitro;* and the work of Allgöwer, Blocker, & Engley (9) on immunologic aspects of homografts in rabbits Douglas (32) found that large living grafts of both human amnion and chorion when applied to fresh wounds of dogs and humans have been proven to take and remain viable under the conditions and during the periods of time described. Douglas does not advise the wide use of these membranes on extensive wound surfaces until more advanced studies are completed.

Numerous observations concerning the use of the adrenocorticotropic hormones and cortisone in skin grafting include those of Edwards *et al.* (34) These authors reported a case of a nine year old boy who seemed to be sensitive to his own skin However, grafts were successful under ACTH therapy, with permanent survival of the grafts Morgan (70) studied the influence of cortisone on the survival of homografts of skin in the rabbit. This author reported that in the control animals the grafts were all necrotic by the tenth ot the twelfth day. In thirteen of the twenty-two animals, there was some delay in destruction of the grafts Weisman and associates (107) reported on the failure of adrenal cortical hormones to prolong the survival of homologous skin grafts in guinea pigs. Conway & Stark (26) and Conway and co-workers (27) reported unsuccessful results when homografts of skin were applied to a patient with therapeutically effective doses of ACTH. Baxter & Entin (14) made a clinical study of the fate of homografts in man. They studied the effects of repeated dosage from the same donor, and of refrigeration on these grafts. As far as the first of these two

Raker *et al.* (85) studied the subject from a different angle. These Boston authors administered ACTH in an attempt to determine if the need for fluid therapy of the burned patient is diminished. They found that as far as the need of the burned patient for immediate fluid therapy is concerned, there is no reason to recommend the use of ACTH. In a subsequent study, Wight and co-workers (109) studied 24 dogs which were subjected to cannulation of the hind leg lymphatics and burning of the cannulated extremities at 90 degrees C. for 10 sec. Seven dogs were treated with cortisone and nine with corticotropin, the remainder serving as controls. No consistent effect of the hormones was demonstrated on the rate of edema formation, the lymph flow, the lymph protein concentration, the serum-protein concentration, or the hematocrit level. They concluded,

We have found no evidence that the abnormal capillary permeability engendered by a burn is influenced by either corticotropin or cortisone These experiments negate the claims recently made that these hormones are plasma and fluid sparers in the burned patient.

Evans & Butterfield (41) studied the stress response in the severely burned. They concluded that analyses on four burned patients served to support the hypothesis that such a stress response may be largely from the release of a substance with the properties of Compound F from the adrenal cortex. The syndrome of burn-stress pseudodiabetes was described. Their general conclusion was that more studies of the natural stress response following injury in the severely burned patient are needed before hormone therapy in the acute phase after burns can be considered to be on a truly rational basis.

Dougherty & Schneebeli (31) studied the role of cortisone in the regulation of inflammation. They suggested that an antiphlogistic reaction of cortisone accounts for the capacity of this hormone to minimize the consequences of a wide variety of unrelated inflammation producing stimuli. Sevitt (92) studied the eosinophil changes in burned patients. Soon after burning, the eosinophil count falls and reaches low or zero values in a few hours. The eosinopenia, which may persist for a few days, lasts longer in the more extensively burned patients. In four patients an early eosinophilia was found, and in two it was associated with intercurrent infection. In five patients a delayed eosinophilia began four to six weeks after burning. In five out of eight fatally burned patients there was marked eosinophilia, demonstrating probable hyperactivity of the adrenal cortex It would seem to this reviewer, as it has to some others, that if the adrenal cortex is hyperactive even in fatal burns, hormonal therapy may not be advisable.

Early Skin Grafting

The use of ACTH and of cortisone in homografting.—In grafting third degree burns, which, by definition, are those with raw surfaces, autografts are generally preferable. In some severe burns, however, homografts may prove

at many points which cannot be covered in this short review. A number of the outstanding miscellaneous advances, however, will be summarized in the following paragraphs. An excellent review, by Evans (40) touched on many of the questions that we have discussed in this chapter. Walker (105 of the University of Pennsylvania has similarly reviewed "The Problem of the Extensive Cutaneous Burns." An annotated bibliography compiled by Baer (13) on the pathology and physiology of burns, 1942–1951, appeared in June 1952 A brochure containing the collected papers of the Surgical Research Unit at Brooke Army Medical Center has been put out by Amspacher (11).

Effects of radiation.—Chanutin, Ludewig & Lentz (23) studied the influence of thermal injury and a combination of thermal injury and x-irradiation on the serum iron concentration and on the iron contents of the liver, spleen, and kidney. In the liver and the spleen, mild thermal injury increases the iron content of these organs and at the same time causes a hypoferremia. The additional injury, imposed by x-irradiation, causes a transient hyperferremia and makes the increase in the deposition of iron in the spleen and liver more prolonged. Brooks *et al.* (20) studied the effects of burns in combination with the radiation on mortality response to thermal burns in dogs. Irradiation increased the mortality and, interestingly enough, penicillin therapy showed a marked beneficial influence in reducing sharply the mortality of experimental animals receiving the combined thermal and radiation injury.

Flash burns.—The workers from the Department of Surgery of the University of Rochester have continued their work on flash burns. In one paper Morton, Kingsley & Pearse (71) studied threshold burns following flash injury They described a modification of the carbon arc as a source of reproducible high intensity, short duration burns In another paper (72), the same authors studied the protective effects of fabrics They found that the color of the fabric was the single most important quality in determining the amount of skin protection. Light colored fabrics were more protective than darker ones In all experiments, burns occurred even when there was no apparent damage to the surface of the material touching the animal.

Sludged blood.—The occurrence of sludged blood following severe thermal burns has been described by Brooks and associates (19). A decreased rate of flow to as little as one-third the pre-burn rate was observed in their experiments on rabbits and dogs, and in certain patients at the bedside. A decreased rate of flow was the most definite and most easily observed change in the circulating blood after burns. On the basis of their experiments, they concluded that this sludging process must be vigorously investigated before one can determine a reasonable and adequate treatment for burned human beings. In another paper, Knisely (53) presented an extensive annotated bibliography on sludged blood.

Fundamental studies.—Ever since tannic acid was implicated in the causation of central necrosis of the liver following burns, this subject has been one of interest. Mosesson *et al.* (73) reported additional experiments on this subject. Ellenberg & Osserman (36) came out, however, with experiments

points is concerned, their results tended to support the theory of active immunity in explaining the failure of skin homografts. When successive sets of homografts were applied from the same donor, the survival times of the later grafts progressively decreased. Refrigeration shortened the survival of homografts, irrespective of the duration of storage.

Trusler, Glanz & Bauer (101); May, Oakey & Pilling (61); and McNichol (64) all found that ACTH was not of value in prolonging the life of homografts. McNichol stated categorically, "ACTH in no way prolonged the survival of a large homograft, which originally had 'taken' completely, beyond the average survival of homografts without ACTH." Bishop, Beal & Longmire (15) also found that preoperative administration of ACTH to two skin homograft donors and recipients with continuation of ACTH administration postoperatively to the recipients did not prolong the survival time of the homografts. The preoperative administration of ACTH to both donors and recipients did not interfere with the initial take of either the homografts or autografts or the permanent survival of the autografts Autogenous epithelization of granulating areas may have been retarded by ACTH therapy. Cortisone was unsuccessful in these authors' experiments in prolonging the survival time of a skin homograft in the one patient to whom they administered this hormone.

Randall, Brown & McDowell (86, 87) presented a technique of studying skin homografts which closely simulates the situation in the human being where the graft takes primarily, but then shows dissolution. The technique involves the use of mice of two different pure strains. Using this method, ACTH and cortisone were found to have only insignificant effects Marrangoni (60) found that ACTH and cortisone do not prolong the survival of isografts. Cannon & Longmire (22) observed occasional takes of skin homografts in chickens a few days old ACTH had no effect on these grafts but cortisone increased the incidence of survival of the grafts from 6 per cent to 20 per cent, and the increased incidence of survival persisted at least six weeks after discontinuation of the drug therapy. Allen *et al.* (8) found that ACTH has no effect on the survival of skin homografts in rabbits.

Brown (21) epitomized the belief of many surgeons concerning the use of ACTH He stated,

> If foreign skin would survive permanently, we could surmount one of the greatest obstacles. If ACTH can accomplish this, as has been suggested, it will be the most valuable contribution to the problem. It is hardly possible, however, that ACTH will make us all alike which is what we are saying when we say that homografts will survive. There does seem to be a good deal of confusion in the use and even in the terminology of homografts, but so far no substantial series of permanently surviving grafts has been forthcoming Homografts will take and grow with or without hormones or antihistamines and independent of blood grouping, but permanent survival in consistent use is yet to be proven

Miscellaneous Advances

Advances on the frontiers of knowledge concerning burns have proceeded

more extensive changes after rapid thawing, while 15 cases showed greater changes, mainly degenerative, after slow thawing.

Entin & Baxter (38) used rats to study this problem experimentally. The hind legs of these animals were used for the production of a reproducible standard cold injury. Large numbers of animals were studied and the results were evaluated by statistical analysis. Supplementary experiments were carried out on dogs, which provided a bulk of tissue comparable to man. These authors found that rapid thawing in a warm bath at 35 degrees C. to 45 degrees C. was most effective in reducing the loss of limb. Slow thawing at room temperature prolonged the period of cooling and increased the circulatory embarrassment These authors concluded that the mode of action of rapid thawing depends on a number of physiologic changes, including shortening the period of anoxia and ischemia, and the positive production of vasodilatation. They stated that to be most effective, the thawing must be immediate, rapid, penetrating, and should not exceed the normal temperature of the part by more than a few degrees. Pichotka & Lewis (77) performed somewhat similar and extensive experiments on rabbits. These authors found that rapid thawing of frozen legs in water at 42 degrees C. for 5 to 8 min almost entirely prevented cutaneous necrosis after exposure to minus 12 degrees C. to minus 15 degrees C. for 30 min Spontaneous rewarming in air after the same standard injuries resulted in superficial necrosis in 20 to 90 per cent of cases. The extent of muscular necrosis is also definitely decreased by rapid thawing but not as much so as in the case of cutaneous necrosis Prolonged rewarming with water at 42 degrees C. for 1 hr. was as beneficial as rapid thawing for only 5 to 8 min. These results of Pichotka & Lewis are further referred to in the U. S. Air Force Medical Service Digest (33).

Early and Late Local Care

Value of sympathectomy.—The whole question of the use of sympathectomy in the treatment of frostbite is unsettled. Many of the frostbite injuries occur at places where sympathectomy is not possible of accomplishment. By the time the injuries reach large medical centers, the surgeon who performs the sympathectomy does not have a first hand impression of the original findings. Furthermore, frostbite injuries vary greatly in intensity among themselves and even individuals with great experience cannot tell in all instances, even in the controlled and untreated cases, what the prognosis will be or what the severity of the injury is Shumacker (94) reported on the use of 33 sympathectomies performed in 20 patients Two of the patients were treated early, within five to seven days, and in both instances Shumacker believed the results were good. In 10 patients the sympathectomy was done at an intermediate stage from 2 to 11 months after frostbite, Again, the results were good or excellent in all instances. Finally, in eight patients sympathectomy was used in the late treatment from 3 to 22 years after the original injury. The conclusions of this author are that sympathectomy has a definite place

which indicate that shock alone will frequently give rise to central liver cell necrosis.

Haynes, DeBakey & Denman (48) have reported interesting renal function studies on severely burned patients. The characteristic response to a burn includes an increased glomerular filtration rate, a normal effective renal plasma flow, and an increased filtration fraction. Tubular function, on the other hand, appeared to be normal.

FREEZING

Freezing may differ from burns in one practical respect The patient is often burned over a sufficient surface of the body to cause burn shock and general changes that result in death as a result of the burn. In the case of freezing, however, it is practically impossible for a patient to have so much of the body frozen that shock will be produced without the patient long since having succumbed to exposure. In clinical practice, we speak of patients with more than 50 per cent of the body surface burned, but few clinicians have seen patients in a viable condition with more than 25 per cent of the body surface frozen.

The problem of freezing and frostbite injuries is a practical one, and the importance of this subject has recently been emphasized by the number of such injuries occurring in the Korean Theatre particularly during the winter of 1950 to 1951. There are many aspects of the subject that deserve comment, but the following items are particularly pertinent at this time.

EARLY LOCAL CARE

Benefit of rapid rewarming.—Adams-Ray & Falconer (3) have studied the pathologico-anatomical changes following rapid and slow thawing in the frozen skin of man This subject is one that has been bandied about for many years and it is popularly believed, particularly by the laity, that rapid thawing is harmful and that rubbing with snow and slow thawing is preferable in the treatment of frostbite and freezing. Harkins & Harmon (47) reported, on the basis of experiments done on rabbits' ears, that the results of rapid thawing are at least as good as those of slow thawing. Adams-Ray & Falconer studied an extremity, usually the leg, in 21 patients in which amputation would have to be done anyway. Most of these patients had arterial deficiency but one was that of a girl, aged 16, with sarcoma. Immediately below the site of the planned amputation incision, freezing with ethyl chloride was done simultaneously on the medial and lateral aspects of the leg. One of these areas was rapidly warmed with warm, moist compresses at 37 degrees C., whereas the other control area was left to warm up gradually [illegible]

[illegible]
between the rapidly warmed and slowly thawed areas. Three cases showed

more extensive changes after rapid thawing, while 15 cases showed greater changes, mainly degenerative, after slow thawing.

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in the intermediate and late treatment of frostbite and related cold injuries He stated that the few observations available for analysis suggest that this treatment may also be a useful measure in the early treatment of certain patients, tending to bring about rapid disappearance of pain, sensitivity, and edema; quicker demarcation of gangrenous areas; and more speedy healing of residudal ulcers Additional careful observations are needed, however, in order to confirm these impression and to outline better the indications for the use of sympathectomy.

Lewis (56) studied the effect of microwave diathermy treatment of frostbite. These experiments were performed on 78 male albino rabbits of which 39 were treated with diathermy and the remainder served as controls. Standard freezing injuries were produced, and the two groups of animals were compared. Lewis concluded that rapid rewarming of frostbitten rabbit legs by means of short wave diathermy resulted in a decrease in the extent of muscle and skin necrosis in comparison to control frostbitten animals thawed at room temperature in air.

Fletcher (43), basing his remarks on recent cases of acute freezing at Sapporo Hokido Island, Japan, stated that he has seen three patients in which lumbar sympathetic block led to marked and rapid improvement. One patient, treated 14 hr. after exposure of four extremities, had bilateral lumbar and stellate blocks The disappearance of cyanosis was definite and progressive, particularly in the legs. Two other patients treated 24 hr. after exposure showed definite improvement in the legs following lumbar sympathectomy.

Benefit of drugs (cortisone, heparin, ergot derivatives, sulfamylon, and hyaluronidase.—Cortisone has been tried in frostbite as it has in practically every other condition. Higgins *et al.* (49) studied the symptomatic and metabolic effects of cortisone in clinical patients with frostbite at the U. S. Naval Hospitial in Oakland, California. In comparison with the control group, these authors found no significant clinical or metabolic effect following the use of the drug. Lewis & Freytag (57), approaching the subject from the experimental aspect, found that cortisone is the doses used in their experiments was not effective in reducing the extent of muscle or skin necrosis in rabbits after two standard local cold injuries

Use of anticoagulants in frostbite has been in vogue for some seven years. Theis, O'Connor & Wahl (98) studied the use of these drugs in 14 patients who were exposed to cold within 24 hr. before treatment was initiated The average duration of exposure was 10 hr. Treatment involved the use of heparin sodium intravenously and bishydroxycoumarin (dicumarol) by mouth These authors stated that the results were gratifying, as only one of the treated patients required local amputation of a finger. They stated that the duration of hospitalization was appreciably reduced and the patients were returned to normal activities more quickly than without such treatment. They concluded that adequate anticoagulant therapy in the acute stage of

frostbite is of great value in reduction of the incidence and extent of gangrene and of the period of disability following such injuries. Pichotka & Lewis (76) studied the use of heparin experimentally on rabbits and found that it did not produce beneficial results under the conditions of their experiments. Shumacker & Lempke (95), on the other hand, stated that intensive anticoagulant therapy is of benefit in the prevention of necrosis after frostbite. Edwards (35) pointed out that whereas anticoagulants may be of value in civilian surgery, they are often of less practical value in military surgery because of associated injuries.

Hoelscher (50) studied the morphological changes in the adrenal cortex of frostbitten rabbits with and without heparin treatment His results are of extreme general interest. His experiments showed that heparin therapy, especially that administered for frostbite during the winter months, caused severe adrenal damage. In severe cold injury, degenerative changes in the adrenal cortex were also observed, and these were increased in severity by the heparin treatment.

[Speaking now of burns, Elrod, McCleery & Ball (37) reported that heparin, in dosage comparable to the ordinary therapeutic regimen, caused a significant increase in the survival time of burned dogs. These authors reported an apparent decrease in the expected hemoconcentration and postulated a theoretical concept suggesting "the chemical alteration, by heparin, of a protein toxin."]

Hurley *et al.* (52) studied the use of dihydrogenated alkaloids of ergot in the treatment of experimental frostbite, using tail loss in rats as a criterion of the benefits of treatment. These authors found that both heparin and dihydrogenated alkaloids of ergot used together were beneficial and that their favorable action was largely a result of the action of the vasodilator and not of that of the anticoagulant. Hurley & Buchanan (51), in their latest available paper on the subject, reported the effect of hydergine, a combination of dihydrogenated ergot alkaloids on white rats either before or after freezing. The therapeutic results in the treated groups, when compared with the end results in the control groups, showed a statistically significant reduction of extent of tail loss in the treated animals.

Pichotka & Lewis (75) pointed out that one of the major problems encountered in investigations on experimental frostbite is the prevention of infection in the frozen tissue Without prophylactic treatment, infection occurs in practically every instance, the infection particularly being ascribable to *pseudomonas aeruginosa* (*Bacillus pyocyaneus*). Sulfamylon and penicillin were studied and compared; in both instances the drug being applied locally in the form of ointment. Thirty of 78 animals treated with penicillin ointment developed infection, whereas only 4 of 212 animals with the same degree of cold injury and treated with 3 per cent sulfamylon ointment developed local infection with *pseudomonas aeruginosa*. The authors concluded that sulfamylon is superior to penicillin in its effect on *pseudomonas*

in the intermediate and late treatment of frostbite and related cold injuries. He stated that the few observations available for analysis suggest that this treatment may also be a useful measure in the early treatment of certain patients, tending to bring about rapid disappearance of pain, sensitivity, and edema; quicker demarcation of gangrenous areas; and more speedy healing of residudal ulcers. Additional careful observations are needed, however, in order to confirm these impression and to outline better the indications for the use of sympathectomy.

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fundamental importance and indicate the fundamental similarity of the body response to various types of injury.

Lewis & Thompson (59) have shown that local cold injury must be added to the list of conditions resulting in renal tubular degeneration. The degenerative changes were not necessarily confined to the lower portion of the nephron. Severe renal lesions can be produced in rabbits by exposure to a degree of local cold injury which results in mild muscle atrophy but without necrosis.

Conclusions

Burns.—(*a*) Both the exposure method and the occlusive dressing technic of early local treatment of burns have their respective indications and advantages; (*b*) Whole blood, plasma, saline, and plasma volume expanders are useful in the general supportive therapy of burns; (*c*) ACTH and cortisone are of doubtful value in the general treatment of burns; (*d*) ACTH is of no proven value and cortisone of possible academic, but not practical, value in increasing the duration of take of skin homografts in the treatment of third degree burns.

Freezing.—(*a*) Rapid rewarming is of value in the restoration of a frozen limb, (*b*) Certain drugs (ergot derivatives and sulfamylon) may be of use in the treatment of frostbite, but their clinical value is yet to be proven.

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aeruginosa infections under these circumstances, and that it is possible to control the infection due to *pseudomonas aeruginosa* in experimental frostbite by daily local applications of sulfamylon ointment.

Pirozynski & Webster (80) studied the effect of hyaluronidase on the edema following experimental cold injury. These authors found that tissue which is edematous after cold injury shows a subsidence of the edema after local injections of the enzyme hyaluronidase. The evacuation of this edema did not seem to influence the gangrene, as this complication developed simultaneously and equally in treated and control experiments. The authors concluded, therefore, that tissue necrosis is not primarily related to the accumulation of edema in the region of cold injury.

Fundamental Studies

Much remains to be done in elucidating practical and fundamental problems concerning treatment of frostbite injuries Irwin & Schultz (52a) have given a good outline of the general hygienic care of these patients. At the more fundamental level, Lewis (55) performed experimental studies on rabbits concerning the pathogenesis of muscle necrosis resulting from experimental local cold injury. This author pointed out that degenerative changes in muscle are produced almost immediately after exposure to frostbite. He believed that such early changes cannot be ascribed to ischemia from stasis, sludging of blood, or thrombosis, since complete ischemia induced by the application of a tourniquet failed to result in signs of muscle degeneration. The primary cause of the muscle necrosis must, therefore, be the direct action of cold on the tissue cells. Pichotka, Lewis & Freytag (78), in an excellent study, have shown effects of different temperatures on muscle and skin, and have outlined three characteristic degrees of injury which result from exposure to from plus 5 degrees to minus 40 degrees C. for 30 min. (*a*) Functional changes occurred from exposure to plus 5 down to minus 5 degrees C., and such changes in general were temporary, although some instances of muscle atrophy resulted; (*b*) Atrophy and isolated necrosis of muscle occurred from exposures to minus 10 to minus 12 degrees C., (*c*) Skin necrosis plus the abnormalities noted under (*a*) and (*b*) occurred from exposures to temperatures below minus 12 degrees C. Pichotka, Lewis & Luft (79) studied the effects of associated general hypoxia on local cold injury They found that the hypoxia given in a preparatory period up to 30 min. before or during exposure to cold did not influence the extent of necrosis. Hypoxia after cold injury or in instances where the preparatory hypoxic period exceeded 30 min. had a definite influence on the extent of necrosis

Lewis & Moen (58) have reported some very interesting studies concerning the relative effects of cold, heat, and ischemia. They found that these three injuries produce the same pathologic changes of muscle, and the application time acquired for each to produce like changes is different. Heat requires the least time and ischemia the greatest, with cold occupying a time of action between these two. These studies of Lewis & Moen are of great

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RADIOLOGY[1]

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The growth of Radiology as a science, particularly its application to the practice of medicine, has been phenomenal. It recognizes no barriers and has cut through all medical fields, including the basic sciences. There is probably no branch of medicine in which radiological methods do not have a definite place; possibly psychiatry excepted The reviewer "begs off" the task of an anthology or compilation of every paper or contribution published which touches on radiology, without the slightest implication of trivializing these efforts, the very foundation of advance in scientific knowledge. Instead, with editorial acquiescence, an attempt will be made to present the trends and various lines of progress in the field in recent years, considering in greater detail the reviewer's own segment of the subject and with full expression of his own views and prejudices!

Two trends, dominant in recent years, continue to be reflected in contemporary radiologic writings: First a tendency to recapitualate, and secondly more and more emphasis on quantitative analysis.

RADIOLOGY IN DIAGNOSIS

Cardiovascular System

With the availability of modern cardiac surgery acting as stimulus, publications on the roentgen aspects of congenital heart disease in infancy, childhood, and adults have flooded the literature. Surgery is available and the indications are fairly well defined for the patent ductus arteriosus, coarctation of the aorta, anomalies of the aortic arch, and tetralogy of Fallot Operative procedures have also been devised for closing auricular septal defects and compensating, as a palliative procedure, the malformations of congenital transposition of the great vessels and tricuspid atresia The indications, however, for the latter group are still not well defined and discussion thereof will always include philosophic aspects.

The exact role that the roentgen examination is going to play in the detection or the diagnosis of congenital heart lesions is still difficult to predict. Rarely can a specific anatomical diagnosis be made by roentgenographic examination alone. The final clinical diagnosis must be left to an exact correlation of the history, physical findings, fluoroscopic and x-ray examination, electrocardiogram and some laboratory procedures. Many classifications for congenital malformations of the heart have been published A strictly radiographic classification will never prove entirely satisfactory The inherent limitations of the technique do not preclude its use to optimum advantage.

[1] The survey of literature pertaining to this chapter was concluded in September, 1952.

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derlines the necessity of weighing the operative risk against the potentiality of this relatively benign disease.

Septal defects—The simple isolated auricular septal defect, if of sufficient magnitude, produces roentgenographic right-sided enlargement of the heart with ventricular hypertrophy by electrocardiogram, while in the case of the isolated ventricular septal defect it is not uncommon in childhood to find anatomical evidence of right ventricular enlargement by x-ray with predominant left ventricular hypertrophy by electrocardiogram. This may be a helpful sign in the differential diagnosis If the interventricular septal defect shunts considerable volume of blood from left to right this will sooner or later be reflected by increased prominence of the pulmonary vascular markings throughout both lungs recognizable by x-ray.

Surgical closure of the auricular septal defect is now possible. The hemodynamics of experimentally produced interauricular septal defects in animals have been studied for many years. The response of the human to closure of a septal defect appears to be quite different from the response resulting from closure of an experimentally produced defect An explanation lies in the adaptive changes that have taken place secondary to the congenital lesion, probably mainly extra-cardiac, in the peripheral pulmonary and systemic arterial system. The relatively rare isolated, simple, or small ventricular septal defect (Maladie de Roger) is still not amenable to surgery in the human.

Patent ductus arteriosus.—It was formerly believed that 15 per cent of children and adults with persistent patency of the ductus showed no structural abnormality of the heart recognizable by roentgenoscopic or x-ray examination. Each year it is becoming more evident that this figure is actually considerably higher [Gross & Hubbard (1), Gross (2), and Sweet & Scannell (3)] The conformity of the x-ray appearance of the heart in patent ductus arteriosus, high or large ventricular septal defects and pulmonary aortic fenestrations (a congenital communication or fenestrum between the ascending aorta and main pulmonary artery), is now well established The sites of these three anatomic malformations are only a few centimeters removed from one another, yet they all shunt blood from the "outflow tract" of the left side of the heart into the pulmonary artery, thus placing the same load on the heart and producing an identical cardiac configuration. The physiological diagnosis of a left-to-right shunt may be accurately made by x-ray, but the exact anatomical point of crossover may frequently not be defined. Here the newer techniques of cardiac catheterization and retrograde aortography have proven of great value in exact anatomical localization of the defect. An increasing number of case reports have appeared confirming persistent patency of the ductus arteriosus in the absence of a typical machinery to-and-fro murmur, formerly the *sine qua non* of the diagnosis Those without typical murmur have, in the experience of the reviewer, fallen into three categories to date (*a*) excessively large ducti, (*b*) pulmonary hypertension,

It is now a relatively simple matter to classify the majority of congenital cardiac abnormalities on a broad physiological basis into categories which will permit a practical therapeutic program. This includes the segregation of the surgically correctible lesions. By close cooperation of the cardiologist, radiologist, and surgeon a satisfactory working diagnosis may now be arrived at in approximately 85 per cent of patients over the age of two years with cardiac malformations. It is only for the remaining patients that it may be necessary to call upon the more complicated methods of diagnoses, such as angiocardiography and cardiac catheterization. The size and shape of the heart and the character of its beat is a product of the load, past and present. The radiologist judges the heart by its appearance and behavior.

At birth the shape of the heart reflects its function during fetal circulation; the right and left ventricles are of comparable size, the myocardium of equal thickness. It is only some time after birth, following closure of the ductus and foramen ovale, that the heart reveals the increased load of the higher pressures of the systemic circulation and assumes a more adult shape with left ventricular prominence.

Abnormalities of the heart valves, or defects altering the course of blood flow through the heart will eventually be reflected by alterations in size, shape, or beat of the heart if the load is sufficiently abnormal. Similarly, it must be remembered that congenital defects may exist in the heart and be totally undetectable roentgenographically unless they produce a sufficiently abnormal work load to be reflected in a gross chamber enlargement. Small shunts from the left to right side of the heart, such as seen in some interventricular septal defects, or in auricular septal defects, or patent ductus, may exist throughout childhood without producing a recognizable change in the size, configuration, or character of the beat of the heart, just as a low grade hypertension may be tolerated by an adult over a long period of time with only a mild amount of ventricular hypertrophy. The latter is not necessarily recognized as true enlargement in the cardiac silhouette Keeping these things in mind, many of the recorded inconsistencies become more comprehensible. Much has been added to our knowledge about some of the specific congenital malformations in recent years.

Pulmonic stenosis.—Pure pulmonic stenosis, considered a rarity ten years ago, is now being recognized as among the most common single congenital malformations of the heart. The belief is now becoming established that if the pulmonic stenosis is of the simple valvular type it is usually associated with a post-stenotic dilatation of the pulmonary artery, while the infundibular type of pulmonic stenosis usually presents a hypoplastic main pulmonary artery evidenced by a narrow cardiac "waist." Marked diminution in pulmonary blood flow may be recognized by diminution in the caliber of the vascular markings in the mid-lung fields Collateral circulation in this group of patients has not been observed. Surgery is now available for this malformation, although a mortality rate ranging between 10 to 18 per cent un-

right ventricle, thus producing a configuration indistinguishable from the tetralogy of Fallot Children with congenital tricuspid atresia may be handicapped as a result of: (a) inadequate pulmonary blood flow because of too small a left-to-right shunt by the small caliber or closure of the ductus arteriosus or (b) diminished or inadequate cardiac output resulting from an auricular septal defect too small to be consistent with life. Thus, it appears that the single surgical procedure of adding a left-to-right shunt to increase pulmonary blood flow as done in the tetralogies will not necessarily improve all cases of tricuspid atresia. If those with the small auricular septal defects are to be improved, enlargement of the defect would appear to be a prerequisite In the light of present knowledge, the radiologist may offer more information regarding the size of this abnormality.

Transposition of the great vessels—In complete transposition of the great vessels the aorta arises from the right ventricle and the pulmonary artery from the left ventricle. There are numerous variations from this extreme pattern with partial overriding of the two ventricles by one or both of the vessels Many of these malformations now travel in medical parlance under proper names, helping to obscure the anatomical identity, rather than emphasizing their kinship based on the common denominator that in all these cases the basic malformation is the abnormal take off of the major vessels [Abrams *et al* (6)] Few generalizations about the hearts with transpositions are valid. This is because the clinical aspects, including the course of the disease, the murmurs, the EKG findings, and in particular the roentgenographic appearance of the heart will be determined by the compensatory or associated lesions It is to be emphasized that beside the abnormal relationship of the base of the aortic and pulmonary artery, a typical radiologic configuration of transposition will not exist. One must think in terms of transposition compensated with auricular septal defect and patent ductus, or transposition with ventricular septal defect, etc and, equally important, the size of these defects. This permits a great deal of latitude as is well-evidenced by the clinical features of these patients, in that 86 per cent die by the end of the first year, although patients have been reported who have lived to the age of 56 years without significant physical limitations

Surgical treatment is directed at improving the compensatory mechanism, where indicated Blalock & Hanlon (7) have introduced a number of operative attacks. The operative mortality is discouragingly high, perhaps justified by the extremely poor prognosis presented by patients with untreated disease.

Aortic arch anomalies.—Abnormalities of the aortic arch and its branches continue to be reported by radiologists The true vascular rings, in which connecting vessels form a complete circle around the trachea and esophagus, are most apt to produce symptoms by actual compression of these structures.

usually associated with either a large or longstanding ductus, with occasional reversal of the shunt, [Myers *et al.* (4)] and (*c*) cardiac failure.

CONGENITAL MALFORMATIONS WITH EARLY CYANOSIS

The single most rewarding roentgenographic sign for classifying the cyanotic group is the recognition of increased or diminished pulmonary blood flow as judged by the caliber of the pulmonary vascular markings on the roentgenogram. The tetralogy of Fallot and pure tricuspid atresias will evidence diminution in pulmonary blood flow by lack of prominence of the pulmonary vascular markings usually best recognized in the mid lung field. The truncus communis will invariably present pulmonary vascular engorgement, as will most of the remaining cyanotic heart groups unassociated with pulmonic stenosis. The literature reflects an increasing awareness that the tetralogy of Fallot (anatomically a pulmonic stenosis with the aorta overriding both the right and left ventricles through a high ventricular septal defect) varies considerably in appearance and behavior. The symptoms in patients with this malformation and the degree in which the heart deviates from the normal appearance is really a quantitative matter and varies according to the interplay of the two basic congenital lesions, namely, the pulmonary stenosis and the overriding aorta. The one extreme is a complete pulmonary atresia with a markedly overriding aorta giving a classic *coeur en sabot* appearance in which the aorta is the only vessel functionally arising from the heart (so-called, pseudotruncus) and in this case the lung receives blood entirely via the bronchial arteries. At the other extreme there is the low grade pulmonic stenosis with a minimal overriding of the aorta, in which case cyanosis will be mild and the symptoms will be minimal Collateral circulation for the lungs through the bronchial arteries when developed can now be recognized roentgenographically. The main feature of this collateral circulation is a distinctive pattern of the vascular markings in that the bronchial arteries pursue a considerably more tortuous course, lacking the linear radial distribution of the pulmonary arteries. They also do not appear to emanate from a central point in the hili.

Patients with tetralogy of Fallot respond well to palliative surgery, if the primary pulmonary blood flow is grossly deficient and the collateral circulation is not already well developed. Surgery is directed at increasing the pulmonary blood flow by (*a*) an artificial arterial-pulmonic anastomosis (Blalock procedure), (*b*) aortic-pulmonic anastomosis (Pott's procedure), or (*c*) direct attack on the pulmonic stenosis (Brock procedure).

Tricuspid atresia.—Congenital tricuspid atresia has received increasing attention as it is a lesion amenable to the recently acquired surgical techniques The configuration of the heart in tricuspid atresia is determined by the type of associated or compensatory lesions which must of necessity be present if the condition is compatible with life (5). The most common compensatory abnormalities are persistence of the normal fetal channels, namely, the auricular septal defect and the patent ductus arteriosus. The size of the

Patients with little or no evident regurgitation, but with definite x-ray signs of pulmonary engorgement should be considered for operation if active rheumatic carditis and bacterial endocarditis can be excluded [Sweet & Scannell (3), Harkin *et al* (13)]. The significance of these diagnostic and therapeutic procedures for the mitral stenotic is testified by the post-operative follow-up figures on 352 patients· Operative mortality, 15 per cent; clinical "improvement" in the "majority," often "dramatic" [Bland (14)]

Angiocardiography—There has been increasing emphasis on the use of the intracardiac catheter and the injection of contrast media into the vascular channels Although the value of these techniques in the research laboratory is testified by their contribution to our knowledge of cardiac physiology, their place in routine clinical work is still to be determined

Sussman & Brahms (15) fill a great need in their presentation of the normal cardiovascular angiogram in the adult and discussion of common errors in interpretation. The illustrations represent a beautiful demonstration of normal intracardiac anatomy, but the presentation also permits further clarification of the limitations of cardiac angiography which have not been sufficiently stressed in the literature. Among these are: (*a*) A minimum concentration of diodrast is necessary at a given time in the circulation to be visualized on the films. Any portion of the heart not containing this requisite concentration will not be demonstrated Thus, minute shunts or minimal overriding of the vessels will be overlooked by this method; (*b*) certain chambers may be opacified for only a fraction of the cardiac cycle. Therefore, the speed of exposure and frequency of exposure become exceedingly important. The minimal practical requirement for a serialographic machine appears to be 10 to 12 films in 8 sec In general, one may say right-to-left intracardiac shunts of moderate magnitude may be well visualized by angiocardiography, and left-to-right intracardiac shunts are better demonstrated by intracardiac catheterization. The catheter has not always proven to be entirely accurate in localization of the left-to-right intracardiac or extracardiac shunts, a problem which arises in differentiating the high interventricular septal defect from the patent ductus arteriosus Left-to-right extracardiac shunts are usually best shown by retrograde injection of the carotid arteries, which, however, is definitely a surgical procedure Angiocardiography failed to give the desired information in over 35 per cent of adults with suspected lesions of the left heart and aorta [Sutton *et al* (16)]. The percentage of failures in children should not run quite as high. Angiocardiography failed to establish a diagnosis in three patients with complete transposition of the great vessels, while in 10 remaining cases with the same deformity, all proven at autopsy, the diagnosis was clinically suspected prior to angiography [Cooley & Sloan (17)]

Over 300 translumbar aortic punctures, in patients of all ages, are reported by Smith *et al.* (18), with injection of a radio-opaque medium without a single significant complication. This method of visualizing the aorta and branches is of distinct value in the differential diagnosis of some abdominal arterial occlusive lesions, including impaired renal circulation and aneurysms

The reader is reminded that the majority of constricting vascular rings produce symptoms referable either to the trachea or esophagus, that they are not necessarily limited to childhood, and that symptoms are almost invariably exacerbated by feeding. Anomalous take-offs of single vessels from the aortic arch may also produce compression deformities with symptoms Although these abnormalities are common, the incidence of symptoms is quite low and often not recognized until later in life.

Coarctation of the aorta.—The diagnosis of coarctation of the aorta is usually easily established by clinical means and roentgen examination. Variations in the degree of the stenosis, the length of the narrowed segment, the presence of post-stenotic dilatation and aneurysms are of great importance to the surgeon. Careful roentgen study, including fluoroscopy of the barium filled esophagus, usually indicates the site of the coarctation by an indentation on the left below the arch. If the indentation is excessive, a post-stenotic dilatation is suspected. If multiple indentations in unusual places are noted, or a ring shadow of calcium noted, intercostal aneurysms must be considered. These complications may be dealt with in the majority of cases surgically, the longer coarcted segments and post-stenotic dilatations replaced by grafts [Gross (8)]. The operative mortality is low, 10 per cent in adults and probably less than 5 per cent in children [Gross (9), and Burford (10)]

Shallow bilateral notching of the inferior margins of the ribs is undoubtedly most commonly caused by collateral circulation around an intrathoracic coarctation of the aorta with actual reversal of blood flow in the intercostal vessels below the level of the second or third rib. Despite emphasis on the specificity of this roentgenographic sign, it has been known for sometime that it is not a pathognomonic sign of coarctation of the aorta Neurofibromatosis with multiple nodular lesions of the intercostal nerves, which presumably transmit the normal intercostal pulsations to the rib margins, may produce a similar radiographic appearance. Tetralogy of Fallot has been shown to produce vascular notching in at least two instances, presumably collateral circulation with the bronchial vessels An unusual cause of rib notching is reported in which vascular notching of the inferior rib margins is produced by dilated tortuous intercostal veins, the result of collateral circulation from a long-standing obstruction of the superior vena cava [McCord (11)]

Rheumatic mitral valvular disease—In this disease the radiologist, if skilled at cardiac fluoroscopy, may make a major contribution in helping in the selection of patients for surgery, by observing the contour of the left auricle at fluoroscopy during the cardiac cycle [Elkin *et al* (12)]. Gross systolic (ventricular) expansion of the left auricle is practically pathognomonic of mitral regurgitation Mitral valve disease is now commanding the surgeon's attention, but operative procedures must differ depending upon whether the stenosis or insufficiency dominates. If mitral stenosis predominates direct attack on the mitral valve has now proven to be the most successful surgical procedure to be introduced.

during feedings, particularly if an aspiration type of pneumonitis is also present, the burden of confirmation of the diagnosis is carried primarily by the radiological examination, shared by the endoscopist.

Newborn chest—Radiologists are becoming increasingly aware that the

ologic needs of the infant. The course thereafter appears to be a gradual, and at times aimless, irregular expansion of groups of alveoli lasting normally from three to six days The intrathoracic situation is quite unstable during this period *and to make a pathologic diagnosis from a single instantaneous* x-ray exposure of the chest during the respiratory cycle, even favored with a full inspiration film, is like describing a man's gait when he is standing still!

The reviewer will welcome the day when the roentgenographic chest study includes a series of films taken during a single respiratory cycle, thus yielding physiologic as well as anatomic data. These are beyond the drawing board stage and will replace much now attempted by fluoroscopic examination. The increased size of the heart in initial atelectasis of the newborn and its gradual diminution is again reported [Martin & Friedell (25)], a reflection of the altered intrathoracic pressures incident to lung expansion rather than to separation of the placental vascular bed [Scannon (26)] or transverse position of the heart [Bakwin & Bakwin (27)]. The "cardiac enlargement" seen in initial atelectasis of the newborn is just a more marked example of this mechanism.

Gastrointestinal Tract

Calcium chloride orally in doses as high as 68 gm daily in water or milk is an accepted form of treatment for neonatal tetany. There have been a number of reports of its irritating effect and its precipitation of vomiting It is now fairly well established that calcium chloride in high concentrates given orally in infancy will produce a necrotizing gastritis followed by calcification within the gastric wall recognizable by roentgenogram [Hall (28)].

G. I. ulcers in infants and children—Diagnosis of peptic ulcers in infants and children by roentgenologic methods have been less frequent than found at post-mortem examination Ulcers in the newborn infant differ basically from the chronic peptic ulcer of adulthood In the first place, they are invariably acute and are represented either by multiple minute shallow ulcerations of the mucosa or single ulcers that may rapidly perforate. The lower esophagus is as common a site as the stomach or duodenum. In the duodenum they are usually found in the descending portion rather than in the cap. The ulcers are rarely found as an isolated phenomenon, but more commonly in association with circulatory disturbances of the gastrointestinal tract, sepsis, marasmus, burns, and brain damage The high gastric acidity during the first 48 hr. or so of life *may be a contributing factor. Eighteen infants*

[Shapiro (19)]. It may be helpful in determining, prior to operation, how much an anomalous renal vessel contributes to the circulation of the kidney. With further experience this approach may prove useful in differentiating renal cancer from benign intrarenal cyst [Smith *et al* (18)]. This technique is ideally suited for the study of chronic thrombotic obliteration of the aortic bifurcation (Leriche Syndrome) [Shapiro (19)].

Portal venography, the roentgen demonstration of the venous circulation in the liver during exploratory laparotomy, has received increasing attention [Moore & Bridenbaugh (20) and Child *et al.* (21)]. The findings substantiate the concept of streamlined flow in the portal vein, that is, the blood from the spleen is diverted largely to the left side of the liver while that of the mesenteric veins tend to move to the right.

RESPIRATORY SYSTEM

Trachea.—It is known that the tracheal diameter varies considerably in the different phases of respiration and it appears that in partial obstructions of the respiratory tract above the level of the trachea, such as hypertrophied false vocal cords or redundant aero-epiglottic folds, the variation in tracheal diameter may be considerably exaggerated. In the infant it is roentgenoscopically possible to observe a transient, almost complete, collapse of the trachea during the initiation of inspiration in the presence of laryngeal obstruction. In the young adult it is quite common to see the trachea collapse to half its diameter at the level of the jugular notch during cough in the absence of any externally compressing masses In the older age group, as the tracheal cartilage gradually hardens, these changes are minimal. The average antero-posterior diameter of the newborn tracheal lumen on the lateral roentgenogram has been determined as: 4 5 mm at the level of the fifth cervical, 3 9 at the first thoracic, and 3 5 at the third thoracic vertebra. However, there was a range of from 1 to 7 mm, the latter measurements being at the level of the junction of the neck and thorax This is the first quantitative data ever published on this subject (22). The reviewer feels that in the evaluation of stridor, or respiratory obstruction of tracheal origin, a serialographic tracheogram is desirable in which the trachea is outlined by lipiodol and a series of rapid exposures made during one or two cycles of respiration. It has been possible by this means to demonstrate collapsing tracheas due to lack of intrinsic support of the tracheal wall.

Congenital esophageal atresia is associated with a tracheo-esophageal fistula in 90 per cent of the patients Up to 1948 only two patients, aged six years and four years, with tracheo-esophageal fistula without an associated atresia had been reported which were successfully operated upon.

The first cases of diagnosis and surgical treatment carried out in infancy of tracheoesophageal fistula without esophageal atresia [Leigh *et al* (23) two cases; Ferguson (24) five cases] stand out as another landmark in radiologic diagnosis Although the diagnosis of this lesion should be suspected in an infant who has frequent attacks of choking with or without cyanosis

question of whether the photofluorograph detects a sufficient number of asymptomatic gastric cancers, or their precursors, to make the method of practical value in reducing the death rate from gastric malignancy must be a flat "no." The effort of mass surveys for this type of lesion appears somewhat heroic in view of the post-operative five year survival rate for the country as a whole of approximately 5 per cent

Genito-Urinary System

Failure of an organ system of the body usually reveals itself by localizing symptoms pointing to the organ itself. If the urinary system of an infant or child is defective, however, the first sign may be failure to grow, with no reference to the source of the difficulty as re-emphasized by Silverman (37). The x-ray examination has proven to be exceedingly rewarding in the early recognition of surgically curable deformities of the urinary tract The irreversible renal damage which may result from nonrecognition of these lesions should increase the urgency of urography.

Along the same line Klostermyer & Thompson (38) are timely in their statement that the "radiologist may be the first to suggest the diagnosis of hydrocolpos" in the infant. A preoperative diagnosis leads to the simple corrective procedure of aspiration of the distended vagina rather than an exploratory laparotomy. The x-ray may suggest the diagnosis by the characteristic position of this centrally placed mass rising out of the pelvis and displacing the bladder in a pancake fashion forward and upward as demonstrated by the simple procedure of retrograde cystography.

Observations made by Briney & Hodges (39) on women with stress urinary incontinence are of considerable interest, not so much as an elucidation of the cause, but as a simple demonstration of the anatomical abnormality and possibly an explanation of the mechanics involved. Studies made incidental to intravenous urography reveal a teat-like or pointed base of the radio-opaque bladder in incontinent women in the upright position. Identical changes are observed consistently in multipara with stress incontinence, but not in multipara or women delivered of Cesarean section This deformity is interpreted to be due to failure of support of the internal sphincter by the pelvic floor [Briney & Hodges (39)] In our experience a similar deformity of the bladder is observed in many children with incontinence on the basis of a neuromuscular disturbance

Osseous System

Three more patients showing late irradiation effects in normal tissue following the administration of deep radiation during infancy or early childhood have been added to the medical literature Each of these patients received 4,258, 3,900, and 4,782 r depth doses, to the femur spine, and hard palate respectively at ages varying from four months to nine years. Murphy & Berens (40) conclude:

or newborns with gastrointestinal ulceration found in a nine year period at The Children's Hospital of Michigan in almost two hundred autopsies are reported [Lemak (29)]. This series again emphasizes the high incidence of brain damage (50 per cent) and prematurity (66 per cent) associated with ulceration in the newborn. Post-mortem figures are, however, a poor index of the true incidence as many will represent ulceration during the immediate pre-mortem phase.

After infancy the majority of peptic ulcers are in the duodenal cap and similar in appearance to those of the adult. Thirty children with duodenal ulcer are reported in the routine work of an X-ray Department in a general hospital, and private office, representing 254 children referred for upper gastrointestinal symptoms [Alexander (30)]. The disease is probably more common than generally suspected, but the true incidence is still controversial

The combined medical, roentgenological, and surgical approach to the management of acute upper gastrointestinal bleeding in the adult has convinced many clinical investigators of the accuracy and safety of early roentgen examination of the esophagus, stomach, and duodenum. This is further supported by the experience of two independent groups reporting this year on examinations of over 130 patients [Ritvo *et al.* (31) and Knowles and associates (32)] The x-ray studies were performed as soon as possible after admission to the hospital and individualized according to the patient's condition, an example of the nicety of the radiologists' clinical judgment which pays great dividends. In about 80 per cent the source of bleeding was not only localized, but correctly diagnosed. In no instance was there a complication attributable to roentgen examination.

Patients with symptoms of chronic and recurring indigestion usually aggravated by food, or patients with ulcer-like symptoms, with roentgen findings characterized by a chronic enlargement of the mucosal folds associated with irregular and sluggish peristalsis and limited motility of the gastric wall continue to plague the radiologist. The problem is twofold: First, are the changes those of superficial spreading neoplasm of the stomach, or so-called hypertrophic-gastritis [Deeb & Stilson (33)]? Second, should chronic hypertrophic-gastritis be considered a premalignant lesion? Gastroscopy may be helpful in the differential diagnosis of the first question; it does not answer the second. Carefully studied clinical series still do not yield a definitive answer and permit considerable latitude of opinion on therapy. If x-ray, gastroscopic and clinical findings are equivocal, surgical exploration should not be delayed [Vaughn *et al* (34)]. Others lean more to the left and feel that patients with these x-ray and clinical findings should have a prophylactic gastrostomy for this premalignant lesion [Barden (35)].

While most medical writers are emphasizing the extreme difficulty, at times impossibility, of detecting early malignancy in the stomach by even the most careful and experienced examiners, the final phase of the mammoth project of the application of the photofluorograph as a survey tool in this disease has drawn to a close [Roach *et al* (36)] The answer to the critical

per cent of these patients. The Sturge-Weber syndrome is a neuroangiomatous malformation, the classical manifestations being the associated calcification of the cortex of the brain underlying the intracranial lesions At least 50 per cent of the patients with tuberous sclerosis have similar intracranial calcifications demonstrable roentgenographically. Clinically, patients with tuberous sclerosis present the triad of facial adenoma sebaceum, mental deficiency, and convulsions. It gets its name from the potato-like nodules occurring in the brain substance which constitute the basic pathological lesions. Holt & Dickenson (44) report a series of 43 patients, and in the 30 patients with tuberous sclerosis who had roentgen examination of the hands and feet, 66 per cent showed localized cyst-like areas of bone destruction in the phalanges and appositional periosteal new bone formation along the shafts of the metatarsals and metacarpals, or both They point out for the first time that

> these highly selective osseous lesions in the extremities are so strikingly similar to each other and to the few scattered illustrations in the medical literature that they may be considered valuable aids in the diagnosis of tuberous sclerosis.

Central Nervous System

Calcification of certain intracranial structures may be considered of no pathological significance. They do, however, increase in frequency with advancing age. Such are the calcifications in the pineal gland, petroclinoid ligaments, falx cerebrae, and the glomus of the choroid plexus. These are encountered on the roentgenographic study of normal skulls in such frequency as to serve as important landmarks. They may yield considerable information if shifted from their normal position. Most other calcifications are abnormal and may be associated with intracranial neoplasms, tuberculoma, abscess, toxoplasmosis, cysticercus, or cortical calcification as seen in tuberosclerosis and hemangiomatosis.

As most of the nonpathological calcifications lie within or about the cerebral hemispheres it is of considerable interest that King & Gould (45) report two cases with asymptomatic calcification in the subtentorial region in the dentate nucleus, confirmed at post-mortem It should be added that hypoparathyroidism may produce calcification in the basal ganglia, as well as in the cerebellum Neither of the above two cases had hypoparathyroidism An excellent review of the roentgen aspects of meningiomas is presented by Pendergrass & Perryman (46) These constitute approximately 15 per cent of adult brain tumors, and may rarely occur in childhood. The tumors, although they arise from cell clusters within the villi of the arachnoid, may evidence themselves on the routine films of the skull. Hypervascularity, thinning, erosion, invasion by, and reactive hyperostosis may occur within the skull as a result of the tumor. The percentage of tumors that reach clinically significant proportions and give rise to no x-ray signs is small but significant.

Ever since the introduction of radioactive substances into clinical use,

Hence coincidental radiation in infants or children will induce permanent dramatic tissue changes, manifested by retardation of bone growth, deformity of muscular, bony architecture, atrophy and scarring of skin, and fibrosis of subcutaneous tissues The changes cannot usually be avoided if a clinical cure is the goal of the radiological procedure.

These conclusions are too broad. The relative radiosensitivity of the tumor with respect to the surrounding tissues is not a fixed factor. More quantitative information is desirable in evaluating relative radiosensitivity. Neuroblastoma is an excellent example in which the majority of the patients who survived without complications of treatment received maximum tumor doses of approximately 1,200 r in 10 to 14 days, some followed by a second comparable series in three months (41). More quantitative data are now available regarding the effect of roentgen therapy during infancy and childhood on the growing spine (42). On the basis of these data it would appear that growth disturbances produced by radiation in the human vertebra bears a definite relationship to dosage and a reciprocal relationship to age. It is felt that although roentgen irradiation of an epiphysis is dangerous in that it may be followed by disturbance of growth and development sufficient to produce an ultimate deformity, x-ray therapy may be so directed as to produce the minimal disturbance of growth and development, usually without producing a functional handicap. A case report of a rare disease manifesting itself in infancy and characterized by stippling of the cartilage by minute deposits of calcium is presented by Savignac (43). The secondary ossification centers of the long bones and the primary ossification centers of the tarsus and carpus are usually involved and first recognized by the characteristic roentgen features. This disease is reported under different names in medical literature, such as, hypoplastic fetal chondrodystrophy, dysplasia epiphysialis puncticularis, as well as calcinosis universalis This malformation is a form of chondrodystrophy commonly associated with bilateral congenital cataracts, neuromuscular disturbances, and often retardation of growth. In many of these children the calcifications disappear during early childhood, and the children grow up with a normal osseous system. If there is calcification of the tracheal rings during infancy, however, the prognosis is commonly fatal. Whether this is the result of the rigidity of the trachea or inability to grow is a matter of speculation. Tuberous sclerosis falls into that category of related congenital malformations which predominately affect ectodermal structures,—skin, nervous system, etc. The group present diverse manifestations, but three particular distribution patterns have been well described and thus constitute a syndrome carrying the name of the original author. These are· Von Recklinghausen's neurofibromatosis, Sturge-Weber's cephalotrigeminal angiomatosis and Bourneville's tuberous sclerosis Neurofibromatosis manifests itself primarily by the nodular new growths along the peripheral nerves with variable neurological deficits and erosive defects produced in the bones by the neurofibromatous elements. Holt & Dickenson (44) have demonstrated skeletal involvement recognizable by x-ray in 30

rate and a vast improvement in palliation in most of the deeper and less accessible cancers. In addition to the slow achievement on a broad front of our older agents, newer weapons of radiation are gradually being mastered.

Grid technique.—A grid is a radiation shield (preferably of lead-rubber) with multiple fenestrations placed over the entrance port of treatment. X-rays enter through the multiple small apertures while the islands of skin and normal tissue in between these openings are protected from the direct x-ray beam. As the depth below the skin increases, the difference in radiation effect tends to be evened out as a result of the divergence of the beam, the secondary and back scattered radiation. In effect, the grid is a sieve and represents multiple small ports which are irradiated simultaneously. This method permits achievement of a greater ionization density in a deep seated tumor for a given amount of radiation on the skin The skin being a limiting dosage factor in adult cancer therapy it almost follows that the grid permits a greater total dosage to be delivered to the tumor and still save the skin and immediate underlying tissues Another benefit of the grid is that the islands of skin protected by the grid from all but back scatter probably permits greater recovery of the skin.

Jaller & Mitchell (49) in England who have been using the grid technique since 1941, and Marks (50) and Harris (51) in this country now report encouraging results in palliative therapy in advanced carcinoma of large volume; the relative effectiveness of the grid is increased with larger ports.

Supervoltage radiation—So-called supervoltage radiation at 2 million volts is now well established in the field of cancer therapy [T[illegible] et al. (52)].

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and the fact that 6000 r may be delivered to a deep seated tumor in 35 days without undue changes in normal tissue [Hare (53)] is sufficient to assure the 2 million volt machine a place in cancer therapy.

Betatron—The betatron is a high powered device for acceleration of free electrons and it yields a very powerful x-ray beam generated at about 24 million volts. The betatron x-ray beam distribution characteristic is such that it spares the skin and superficial tissue at entrance ports even more than the 2 million volt machine, but at the expense of a relatively high exit dose in most anatomic areas. Harney and co-workers (54) report preliminary clinical trials of the betatron with encouraging responses

Radiobiology and Isotopes in Medicine

The subcommittee on Radiobiology of the Committee on Nuclear Science of the National Research Council limited their 1950 meeting to an examination of the fundamental concepts of the radiation effects on living cells. Although not published until 1952 (55) it is excellent reading today to acquaint the outsider with the concepts of the basic research workers in the field of radiology. The radioactive isotopes have been available to the physician for little more than a decade and they bear evidence of becoming the most

investigators hoped that a selective absorption of a radioactive material could be achieved in intracranial neoplasm in sufficient concentration to act as a strong source of irradiation. This would simplify accurate localization of the tumor. Most of the work done in this field has consisted in the tagging of fluorescein, for which all rapidly growing tissues have a particular affinity, with a radioactive tracer (I^{131}). The iodine emits γ-radiation, but earlier work with the Geiger counter revealed the sensitivity to be too low to permit a rapid scanning of the patient's skull. Similar work using P^{32} also does not lend itself well to extracranial measurements as P^{32} is a pure β-ray emitter with a tissue range of only a few millimeters. Ter-Pogossian and co-workers (47) have developed an instrument which is apparently a precision instrument permitting rapid and accurate localization of intracranial lesions which may prove to be a powerful supplement to established methods. The heart of this instrument is a scintillation counter which is exceedingly efficient in the detection of γ-rays. A scintillation counter is a chamber which increases the absorption of the number of particles or rays within the detector by using crystals of fairly high atomic number which emit flashes of light or scintillations when struck by ionizing radiations. The light responses of these crystals are then amplified and pass through electronic circuits to a counting rate meter.

Voris (48) presents a series of carotid and vertebral angiograms, demonstrating the arterial supply and venous drainage of the vascular neoplasm and vascular malformation as well as displacement of the normal arterial system by space occupying lesions. Although this year marks almost a quarter of a century since the introduction of this method, Voris points out it is only since the technique of percutaneous puncture has been perfected that this procedure has become commonplace It is doubtful whether this technique will replace intraventricular air studies in lesions other than suspected aneurysms or arteriovenous malformations with an intracranial bruit.

Radiation Therapy

An analysis of the progress made in every day practice of radiotherapy reveals that there has been a gradual consolidation of our knowledge of the responses of tissue and malignant processes and an increase in the accuracy of the use of the old instruments. The result is a more exact practice of therapeusis. One can predict with some certainty which tumors may be treated satisfactorily and which will show no response. A predetermined dose may be delivered accurately to tumor-bearing tissue. Good objective statistics on the results of these gradual improvements on the general pattern of medicine are sparse, primarily a result of the lack of a uniform standard of reporting. However, reviewing individual reports over a period of a decade it becomes evident that there has been a steady overall improvement in cure rate in the accessible cancers, especially squamous cell carcinoma of skin, cervix, mouth, etc. There also has been a less impressive increased cure

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rewarding single physical instrument for biological investigation. The entire Volume 8 of *British Medical Bulletin* (56) is devoted to isotopes in medicine with good discussions on general principles of assay and standardization counters, autoradiography techniques, etc.

The success of isotopes in radiation therapy has not been comparable with the advances this instrument has brought about in experimental science. Although theory of selective internal radiation of a tumor by the selective up-take of an isotope is appealing, except for the limited successes of iodine and phosphorus this field has been comparatively unproductive

Artificial radioactive sources suitable for interstitial therapy have been developed. Radioactive tantalum in wire form sheathed in platinum has been used as an alternate to radium needles, its flexibility being an advantage in some sites in the body. Radioactive gold grains in platinum are used as substitutes for radon seeds, their main advantage apparently lying in the ease of introduction using a new gun inserter [Sinclair (57)] It has many exponents due to its increased flexibility [Johns *et al.* (58), Green & Ervington (59) and Roberts (60)]. Radioactive cobalt may be used where formerly small radium containers were applicable [Wilson (61), Morton *et al.* (62)]. Radioactive cobalt may now also be used in place of the radium bomb in telecune units offering a radiation beam roughly like a two or three Mev x-ray machine. Four such units are either in use or planned in England. Similar units are undergoing preliminary trials in Canada and the United States [Grimmett and co-workers (63)].

The genetic aspects of radiation risks has assumed top billing among radiobiologists and program committees in recent years Certainly the protection of mankind's germ plasm is a public health problem in its broadest sense. This problem is well discussed by Howard (64), Bonnier (65), and Sparrow *et al.* (66). Information on the genetic effects in humans is so sparse that the problem of sorting out the fundamental findings has hardly arisen.

However, certain features which are unique in this problem are emphasized by Russell (67): (*a*) If genetic damage is done and it is not "all lethal" there is no healing. The only chance of healing lies in the remote possibility of reverse mutation. (*b*) The damage is transmitted to descendants, implicit in the term "genetic" (*c*) The damage may be hidden for a long time, at least one generation, and for the large class of recessive mutations many generations (*d*) There is no threshold dose Thus, says Russell:

> If there is no threshold dose, then a so-called "tolerance" dose cannot be one which produces no genetic effect, but only one which does not add a "serious" increase to the effects that already occur as a result of natural radiation and other causes.

DISEASES OF THE BONES AND JOINTS[1]

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The present trend in diseases of bones and joints continues as a study from the point of view of mechanics and growth and repair of bone. It is interesting to note that at almost every meeting and in every journal there are papers given on such things as fixation with rods, or mushrooms, or lightbulbs, or doorknobs, or other types of prostheses.

Femoral Head Prostheses

The brothers Judet, of France (1), are responsible for much of the talk that we hear now about the different types of prostheses for the femoral head. It is rather interesting that everyone seems to desire to remove femoral heads and replace them with other femoral heads manufactured in some factory far distant from the patient and sent to the physician in the hope that he can find patients into whom he can insert them. Actually, femoral head replacement is a large field and it is only by its use in the hands of many people that we will gradually find out exactly what the limitations are and exactly how useful the procedure is to be.

There has been some evolution in the development of these replacement prostheses just as there has been evolution in the development of the automobile, from the original cars up to the model-T, and then up to the present very fast and highly powered automobiles. So important has this question become that at the Academy of Orthopedic Surgery in Chicago there was a symposium on femoral head prostheses in January 1952. The brothers Judet were present and described what they had done and exactly what the procedure was and what types of prostheses they used. They included a careful description and illustration of the acrylic prosthesis that they had been using. The discussion was carried further and it was found that many of the men in this country were using different types of prostheses of metal and plastics The shapes and sizes of the stems on the prostheses depended upon the men who were using them and who designed them Now we have the lightbulb type of prosthesis (2) and the Minneapolis intramedullary femoral head type (3, 4) etc. These, and others, were on exhibit. Since that time there have been other types that have been called to the attention of surgeons at different meetings and in the literature.

Intramedullary Nails

Another new procedure that comes into the fore with orthopedic surgery is the use of large pieces of metal as intramedullary nails. These are in general

[1] The survey of literature pertaining to this review covers the period November 1951 to November 1952.

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by inserting the nail through a drill hole in the medial side of the proximal tibia at about the level of the tibial tubercle, and then had carried out a closed reduction at the site of fracture, inserting the nail simply by pounding it into place. These results are excellent and it appears that others may be able to learn to do as well, but it is doubtful that this method can be used universally since it appears likely that it will be necessary for the physicians who do these only occasionally to open the fracture site and visualize the nail as it comes into the fracture

The nail used in this instance is a triflanged nail similiar to that used by Smith-Peterson for nailing fractures of the neck of the femur. The nail is, of course, much longer and has two curves so that it will follow the contours of the tibia. The principal problem in the tibia is that it has a narrow medullary canal in its midportion and it is very wide at either end The biggest problem in the use of the nail is the fact that many are started too low and not at the level of the tibial tubercle, resulting in fracturing or splintering of the shaft of the tibia. A careful study of the article by the author (6) and then a check in the anatomy laboratory is suggested in order to be certain that the surgeon can carry out the procedure properly. It would be ideal to observe the insertion of such a nail.

The problem of fractures in and about the region of the hip, the femoral neck fracture, and intertrochanteric fracture, has not yet been completely solved, otherwise there would be no re-introduction of old methods or discussions of newer methods of treatment for this sort of injury (10, 16). At every meeting on fractures these are discussed in detail by men who have considerable experience in treating broken hips. At each meeting there is someone present who is attempting to explain exactly why femoral necks fracture, and principally why they fail to heal. Thus, many of the old problems in fractures continue unsolved

Choice of Materials for Prostheses and Nails

In our discussion of toadstools, lampbulbs, clover-leaf rods, diamond-shaped or hooked rods and all those things, we have to realize that there are various types of metal used (in the main vitallium and stainless steel) and also various types of plastics These plastics present a problem which simply cannot be accepted without research They present us the problem of tissue reaction. Stainless steel and vitallium have been used long enough so that we know the type of reaction to them, if any, and the metals have been refined enough so that we have very little reaction from either of them On the other hand, we do have some evidence to show that there is some reaction to the plastics. Of interest is the fact that one plastic as used may swell about 10 to 12 per cent, as it takes on moisture. The surgeon who uses a prosthesis of this material, fitting it snugly as a femoral head replacement, may be abashed in a day or two to discover that the arthroplasty he had performed has resulted in a potential, if not actual, hip fusion with no motion at the hip because of the swelling of the femoral head. On the other hand, there is

of three or four types. The ordinary Steinman pin is used by some in certain of the smaller of the long bones, or a Kirshner wire or several Kirshner wires in a group. The clover-leaf shaped intramedullary nail, which is the type known as the Kunstcher nail, is used most widely. The type that was made popular by Dr. Rush is the slightly curved long metal rod with a sled-runner point and a hook on the opposite end, somewhat like the crook of a shepherd's staff, is also used. Finally we have the diamond-shaped solid metal rod introduced by Hansen and Street. These all have been used for some time, but in this past year we have had a gradual narrowing down of the indications as to the types of cases in which they should be used. In general, it is felt that in the use of intramedullary nails the selection of the type should be left up to the experience of the individual surgeon.

Intramedullary nails are used principally in femoral shaft fractures (5). It is suggested that they be used first and primarily by the initiate in the transverse mid-shaft fractures without comminution. Later, as the surgeon gains experience, he might try a transverse fracture with some comminution and, in time, use them on slightly oblique fractures and eventually on almost all fractures of the shaft of the femur as experience is gained.

Although the rods used for internal fixation of fractures of the long bones vary in their shape, all are as yet of stainless steel only. The clover-leaf shaped type seems to be the most logical, since it most completely fills the medullary canal at its narrowest portion, the isthmus, starting at the lower end of the proximal one-third of the femur. Since it fills the medullary canal completely it can be likened to a broomstick completely filling a piece of gas pipe and giving support to the pipe whether the pipe is cut transversely or obliquely, whereas a small dowel, within an obliquely cut gas pipe, would permit the ends to slide partly past one another and so allow shortening of the pipe. This does not occur when a type of nail is used which completely fills the meduallary canal at the level at which it is used when an oblique fracture is fixed.

There are suggestions that great caution be used in the presence of infection or in cases of potential infection as expected with an "open fracture" (that is the old-fashioned compound fracture in which the bone comes out through the skin). In such cases it is felt that it is best to apply ordinary means of traction and fixation after cleaning up the wound, and then later insert the nail if there has been no febrile response and no evidence of infection. Following primary healing of the skin wound, two to three weeks after the injury was sustained, intramedullary fixation is suggested.

There have been several very interesting papers presented in the literature and at meetings in this past year on the Lottes (6) type of nail and other nails such as the Rush and the nested V nails (7, 8, 9), which are used for fractures of the tibia by those who have developed this type of nail They have used it now in about 300 cases. A recent survey of this work was presented at the American College of Surgeons, in New York City in September, 1952. It was shown that they had had remarkable success with blind nailing

brought out by Burke (20). He offers the theory that "increasing deformity is the result of soft tissue contracture (or a relative shortening of normal muscles) upon which growth of bone is superimposed." He states this is the etiology of congenital dislocation of the hip. This is startling! The etiology of congenital dislocation of the hip has always been considered by most to be hereditary or a result of position in the uterus, and now we have this theory. The most complete study of congenital dislocation of the hip is given by Haas in his book *Congenital Dislocations of the Hip* (21). To any student who is interested this must be considered a source work and yet there are many things in it which must be carefully added to by collateral reading.

Control of bone growth.—Another problem that enters in diseases of the bones and joints is the treatment of shortness of one of the lower extremities. Whether the shortness is a result of disease in the extremity which is involved or whether there has been overgrowth of the opposite extremity, unequal lower extremities need consideration. An excellent history of the attempts to control bone length beginning with Rizzoli of Bologna as the first to equalize leg lengths deliberately, and then Codivilla, Rizzoli's successor, who carried out surgical procedures to shorten the long leg and even devised a method for lengthening the short leg as early as the end of the nineteenth century, is given by Blount & Zeier (22). Finally, the history carries us along up to the present time and the use of staples to arrest epiphyseal growth on the long side. The beauty of staples is that they can be withdrawn and resumption of growth permitted if it proves necessary.

A careful scrutiny of a situation that has been present in infected bone in children has enabled Truetta (23) to help us come to further conclusions regarding the growth of bone. He stated that when the youngster has an osteomyelitis and the focus of the infection is not near the growth plate, one can expect to see overgrowth of that bone provided the individual is still in the growing age. He carefully studied 100 cases of osteomyelitis and among them found 32 cases with overgrowth and carefully sought the reasons for this. He discovered that in no instance was there any overgrowth of bone if the infection occurred near the metaphyseal area of the long bone, but if the infection was in the diaphysis of the bone, the bone tended to overgrow. This overgrowth continued only for 12 to 18 months. He discovered in every instance the overgrowth occurred when the medullary canal itself was obliterated by the infection. This, he concluded, paralleled the situation in youngsters with over-riding of the bone ends in fractures of the middle of the shaft of the femur, those cases in which overgrowth of bone occurs frequently to overcome the initial shortening by the overlap position. In osteomyelitis of the middle of the shaft of a long bone (only one of two parallel long bones) such as in the tibia and not in the fibula, he discovered there was overgrowth only in the bone with the infection. This, of course, meant that it was not because of any local change of circulation in the extremity as a whole, but rather to some irritation in the specific bone involved. The usual percentage of overgrowth that occurred was about 6 per cent. This over-

some question in the use of the other types of plastics as to whether or not these act as carcinogens and whether or not the patient will eventually have some difficulty with actual malignant changes occurring at the site of the use of such plastics (11). Thus, at the present time it would seem wisest to suggest that we should continue with the tried and true metals, stainless steel and vitallium, in femoral head prosthesis replacements.

At the present time the American Academy of Orthopedic Surgeons and American College of Surgeons both have arranged for committees to study the use of various metals and other types of materials in plates and replacement prostheses. There has been a keen pitting of minds, with excellent arguments on each side, in the use of the various materials. As yet no one is experienced enough and there have not been enough cases reported nor followed long enough to give us the final answer as to whether or not we should eliminate certain of the plastics, or stainless steel, or vitallium, or any of the others.

Treatment in Diseases of Bones and Joints

In driving to a town some distance away, there are probably many possible routes However, there is one best and one fastest route. Yet if all took about the same length of time and all happened to be as easy to travel, it would not matter which route you took except that as time went on you would begin to narrow down to one or two routes and habitually use them. This is exactly the sort of thing that occurs in the treatment of many of the diseases and fractures of bone. When we have many treatments it means simply that there is no single completely effective treatment. There are many innovations introduced each year regarding old problems not completely nor perfectly solved in the past (12 to 15). Injuries about the knee joint and its ligaments are not satisfactorily solved by any means and the trend now is toward surgical repair (16, 17). The reviewer now more critically evaluates end results and has turned to surgery more frequently of late.

Slipping of the femoral capital epiphysis must be considered as this sort of problem (18) Very few months pass when someone does not review the literature and show why a new type of procedure that he has worked out is better than those that have gone before, or how his type of procedure supplements the treatments that had been carried out before Possibly one of the reasons for adding new types of treatment for slipped capital femoral epiphyses is that surgeons are of varying skill and that the cases themselves show considerable differences Badgley & O'Connor (19) discuss the conservative treatment of fractures of the tibial plateau in a refreshing manner, considering the widespread feeling in the recent past that these fractures should be all treated with surgery.

Congenital clubfoot and congenital dislocation of the hip also come into the same category in that they are frequently discussed and there has been no definite and complete answer to all problems that may be present. In fact, the problem is so incompletely answered that we have new evidence

tention is directed to the absence of periosteal bone formation and to the abnormal histological processes taking place in cartilaginous callus This is of importance and it has been used by some to enable greater mobility after anthroplasty and in arthritic conditions (27, 28), in an effort to prevent the formation of new tissue or bone tissue which might retard or impede motion. Variants of cortisone have appeared and have been very promising in the fact that they can be placed directly into joints. According to Hollander (29) they can be injected into the shoulders, hips, knees, ankles, and elbows The injection is carried out quite easily and without any reaction on the part of the patient, in most instances. The patient shows rapid subjective improvement The injections are carried out simply as a palliative rather than a curative procedure but since they do result in improving many of these patients they have added an important, new treatment because the localized arthritis occurs mostly in the weight bearing joints of the lower extremity (hip and knee).

Osteogenesis imperfecta —Each year we are startled by some apparently courageous and yet successful new work that is carried out. Afterward it all appears quite logical, although in many instances it takes years properly to evaluate the early good results that are obtained by the originators of the new treatment. Sofield, Page & Meade (30) have attacked an old problem with a new point of view They have included a newer development, the use of an intramedullary nail in the treatment of an old problem, osteogenesis imperfecta. In their work they completely exposed the long bones which had healed in a curved position following many fractures in the past, osteotomized them at many levels, rearranged the pieces in a relatively straight line, and then threaded them on an intramedullary nail and inserted the intramedullary nail with the beads of bone back into the patients. They have been successful in this without an infection in 17 cases and in several instances have noted that these patients have had no refractures in the extremities so treated. Possibly this is an answer to an old and difficult problem. Also, there is the work of Wright *et al* (31) for therapeutic acceleration of bone age in osteogenesis imperfecta.

Low back syndrome.—The problem of the low back continues to be a severe one. There are still many approaches, there are many new ideas, and many new theories (32, 33, 34). Exactly what role the herniated disc plays in the low back syndrome has not been completely answered, and whether bed rest, manipulation, casting, surgery with fusion of the spine, or removal of the disc or both is superior, remains as yet unanswered.

Considering the cervical spine, Barnes in the *Journal of Bone and Joint Surgery* (35) discusses the mechanism of cord injury without vertebral dislocation. "It is now clear that even when there is no dislocation of the vertebrae a cord may be damaged by a massive extrusion of a disc or by forcible hyperextension of the neck." It was previously believed that the cord injury was caused by transient and often minor dislocation in extension since postmortem examinations revealed a complete rupture of the anterior

growth continues until the medullary canal is opened up again and usually carries on for 12 to 18 months. Quite by accident he discovered that a youngster who had had an osteomyelitis of the humerus later developed a cyst in the humerus in the upper third of the shaft. This was opened and filled with bone chips and inadvertently the medullary canal was closed off with the chips, as is the case in all instances when cysts are filled with bone chips. As the youngster continued to grow there was a disproportionate growth of this humerus and it continued until the medullary canal had again opened up. This was the first instance in which he had actually performed surgery and achieved a resultant overgrowth of the bone other than in the cases of osteomyelitis. Since that time he has attempted to close the medullary canal in long bones in some children and has accomplished this in about 10 cases, with overgrowth in all cases The difficulty at present is that growth soon leaves the blocked area behind and the medullary canal widens and upsets the blocking as the youngster grows. Therefore, to get effective increase in bone length the surgery has to be repeated. The work of Truetta is the most recently reported.

The work of Pease in Chicago (24), with the use of screws of metal or ivory in the metaphyseal region, has resulted in some stimulation of growth and his conclusions, when given several years ago but reported first in January, 1952 in the *Journal of Bone and Joint Surgery*, are a bit at variance with the conclusions of Truetta. Pease still feels that stimulation results in part from increased local vascularity and one cannot as yet state definitely if the surgery done to insert the screws results in the increased vascularity for repair and thus stimulates bone growth. The success of Pease's work seems likely to be resulting from the fact that the screws he uses cross both cortices.

Tendon transplants—Some of the real gems in studies of the diseases of the bones and joints appear in the meetings of the Academy of Orthopedic Surgeons usually held in January. At the meeting in 1952 Kuhlman (25) gave a careful clinical evaluation of all types of tendon transplants for poliomyelitis affecting the lower extremity. This was a classic and very informative It is only by a study of his paper that one can gather all that is important in this subject

Scoliosis.—The study of scoliosis continues, and it is reported upon several times yearly by the men who are most interested in this work and have had the most experience in it, Risser, VanLacham, Cobb, Ullrich, Schmidt and Mayer etc.

ACTH and cortisone—We have had the introduction of ACTH and of cortisone in the last few years. Both have been used extensively for their effect on bones and joints. Cortisone has been used principally for its effect on healing of injuries or surgical wounds Sisson & Hadfield (26) report on the influence of cortisone on the repair of experimental fractures in the rabbit and they report as follows: "at a daily dose level of ten or twenty milligrams per kilogram fractures failed to unite for as long as 21 days, and that all the histological processes of repair in the bone are retarded." In particular, at-

However, there is a very excellent review in the *Journal of Bone and Joint Surgery* in April 1952, where are reviewed all types of chemotherapy then in use for therapy of tuberculosis of the bone (41 to 44). The end results of these studies cannot be ascertained for many years. A recent study on tuberculosis of the bone (45) carried out over a 10 year period in upper New York State showed the results of treatment before the use of penicillin, during the use of penicillin, and then the results with streptomycin and *p*-aminosalicylic acid.

Antibiotics

It is logical to go on and see what effect our present antibiotics have on infections of the bone in general. Pulaski, Hitz & Reiss (46) discuss the use of terramycin and aureomycin in surgical infections, reporting on 200 cases. Of 47 cases with surgical infection aureomycin produced good results in 35. Of 153 cases treated with terramycin, there were 107 with good to excellent results, but the extensively burned cases all failed to respond. The problem there is not simply of antibiosis but a problem of treatment of burns The complete answer to this has apparently not as yet been found.

One must not fail to note that for 1952 there has been a warning issued against the long and continued use of chloramphenicol (47, 48, 49) since the patients so treated tend to have permanent blood changes, agranulocytosis leading eventually to death

Poliomyelitis

Poliomyelitis is more rampant this year than it has ever been, and very timely was the editorial in the *Journal of the American Medical Association* (50) discussing the relationship between inoculations and poliomyelitis. As the result of a survey of the U.S. Public Health Service, "No definite evidence has been found that there has been an increase in the number of cases of poliomyelitis as a result of injections of vaccines, drugs and other medicinal agents."

Rarely has there been evidence that injections for the prevention of diphtheria, whooping cough and possibly tetanus, when given during an epidemic of poliomyelitis, localized the disease as paralysis in the leg or arm into which the inoculation was given. However, there has been no evidence that any other of the types of injections have resulted in localizations of the poliomyelitis in the extremity into which they were given. Since whooping cough, diphtheria and tetanus are diseases of severe consequence in most instances, and the benefits of immunization are great, it is suggested that immunizations against these diseases should be carried out another time of the year than the warm summer months when poliomyelitis is most prevalent. There is, however, no definite need to withhold such immunizations unless the patient is living in an area which is having an epidemic of poliomyelitis in progress. Children under the age of six months can receive such immunizations at any time of the year because of the relative infrequency with which this age group has poliomyelitis

lingitudinal ligament and the intervertebral disc. We had all understood that in cervical cord lesions after trauma without x-ray evidence, that there was a transient dislocation of the neck which snapped back. Taylor (36), in the same journal, describes the mechanism of injury to the spinal cord in the neck without damage to the vertebral column. Here experiments were described to prove that cord injury can be caused by a bulging of the interlaminar ligaments into the spinal canal when the neck is forcibly hyperextended. Now does this mean that we have the same sort of situation occurring in the low back? Is it a fact then, that possibly the interspinal and interlaminar ligaments cause some transient pressure and some injury which results in damage that may be permanent even in the low back? Wallace (37) and others now are producing evidence of multiple disc injuries with symptoms of pressure at various levels in the spinal canal, and simulating many other conditions.

Physical Medicine

No study of diseases of the bones and joints can be complete without including physical medicine Watkins (38) in the *Journal of the American Medical Association* describes the practical application of progressive resistance exercises. His whole aim is to get a rapid increase in muscle strength. Kessler (39), at a later date, discusses rehabilitation in the amputee and here reviews the essentials for properly preparing the amputated stump, the muscles of the extremity, and finally the patient himself for the use of a prosthesis and as nearly normal use of the extremity as possible (*This reviewer wonders why no prosthetic manufacturer has seen fit to produce a temporary prosthesis similar to a crutch made as a pylon which is like an adjustable crutch in its* length and also adjustable in its size at the thigh which could be applied to the patient shortly after his sutures were removed and so permit early ambulation and thus obtain proper shrinkage of the stump more quickly. With such a prosthesis there would be no need to consider rotation since it would be a simple pylon It would enable the surgeon to determine quickly whether or not his patient would be able to resume walking and whether or not it is feasible to purchase an expensive prosthesis. Such a prosthesis would be able to be used again and again on many patients.)

Treatment of Tuberculosis

1951 and 1952 have both shown many developments, not the least among them being the new anti-tuberculosis drugs. These were described originally in all of our newspapers but an editorial in the *Journal of the American Medical Association* (40) described the situation as follows·

> The hydrazine derivatives of isonicotinic acid were described by the newspapers as "wonder drugs" and it is regrettable since the announcements came before thorough, clinical evaluation could be made *We should guard against any such premature claims since the status of these drugs is hardly up to the claims made only six months ago by the newspapers.*

cal diagnosis and therapy is important because this is the beginning of one of the ways in which we will be able to study our patients with malignancy and possibly treat them in the future.

There has been an attempt here to be as inclusive as possible but because of the limited space available it has been impossible to include all the work done in this past year. It has been the attempt on the part of the reviewer to include those things which to him appear to be the most important. This year as in the recent past and probably for many years to come there will be many important developments in diseases of the bones and joints which will need careful study and evaluation.

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William MacDowell (51), Epidemiologist at the American Public Health Service conference in Cleveland said "that significant protection against paralyzing effects of poliomyelitis can be given by inoculating children in epidemic areas with gamma globulin." The comparison of the results is not as yet complete, but it does appear to mean that there will be a desire on the part of many of the parents of youngsters in this country to obtain gamma globulin. The problem of distribution of the limited supply of gamma globulin will be great. The gamma globulin that is used is essentially the same gamma globulin that has been used in the attempt to ameliorate the infection of measles in children who are ill with other diseases at the same time or too weak to withstand a siege of measles.

Bone Grafts

One of the biggest questions as yet unanswered in diseases of the bones and joints is the question of bone grafting (52, 53). Are autogenous bone grafts superior to homogenous bone grafts? Is bone bank bone, whether frozen or put into preservative, as good as bone from the individual who was operated upon? Many are attempting to answer these questions now. One of the most relevant discussions that has been given on this was by Bosworth (54) of New York at the American Academy of Orthopedic Surgeons, when he discussed a study in the use of bone bank bone in spine fusions in tuberculosis. "Unsuccessful fusion occurred almost three times as often with bone bank bone as with autogenous, fresh bone and in later attempts to repair such unsuccessful fusions which are termed 'pseudoarthroses,' the failures with bone bank bone was three times that of fresh, autogenous bone." Kreuz *et al.* (52) discussed the preservation and clinical use of freeze-dried bone. The studies of Ray and associates (53) of histological sections of implants in the anterior chamber to the eye on 35 guinea pigs and rats six weeks after implantation showed

> the fact that homogenous grafts of embryonic bone and autogenous grafts of fracture callus, adult cancellous and cortical bone can survive and proliferate in a suitable

This study along with the other studies we have had on compression of bone (55) and use of preserved bone and freeze-dried bone are helping us to

the availability of the material.

Radioactive Isotopes

Finally, the evaluation of radioactive isotopes (57) as an adjunct to surgi-

OBSTETRICS[1]

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If one stops to survey the recent course of events in obstetrics, the outstanding fact is the striking reduction in mortality of both mother and offspring. For the first time in history a large nation apparently had so few maternal deaths in relation to the number of live births in 1949 that the maternal mortality rate was below one per 1000 (11) Today the hazards incidental to pregnancy and childbirth are at a level which seemed Utopian not many years ago. As recently as 1935, the maternal mortality rate in the United States was 58 per 10,000 live births, the lowest recorded up to that time. Currently the rate is appreciably under 10 per 10,000 nationally, and in large sections of the country it is even less than 5 per 10,000 live births (37).

Hospital Care During Labor

The increase in safety for the mother is a gradual development, as is evident from a glance at the chart which illustrates the rate of reduction of maternal mortality each year since 1935 (Fig 1). A clue to the factors concerned in the decline of maternal mortality from year to year is the evidence of the occurrence of a parallel increase in prenatal care. Safer maternity has resulted in part from the increasing proportion of women utilizing hospital facilities and the services of a physician at childbirth In 1935, only 37 per cent of babies in our country were delivered in a hospital; by 1949 the figure had risen to 87 per cent (Fig 1). Indeed, in towns of population exceeding 2500, about 94 per cent of deliveries were in hospitals in 1949, in contrast to 76 per cent in 1940. At the same time, the proportion of women attended by a midwife dropped since 1935 from 13 per cent to 5 per cent (41). Formerly a serious national problem, maternal mortality is increasingly one for local action in those areas in which maternal mortality rates are still relatively high; in certain states maternal deaths are twice as frequent as in others.

Despite the downward trend of maternal mortality rate, the actual number of deaths associated with childbirth each year is still reckoned by the thousand A total of 4122 maternal deaths, or a rate of more than 11 per day in the United States, was reported in 1948 by the Bureau of the Census in the course of about 3,500,000 births (40). The causes of the maternal deaths listed in this nationwide report were divided almost equally between septicemia (29 per cent); toxemia (28 per cent); and hemorrhage, trauma or shock (33 per cent). The remaining 10 per cent were scattered.

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tion was given as the cause in 19 per cent; toxemia in 13 per cent; cardiovascular disease in 13 per cent, almost three-fourths of them being rheumatic; anesthesia in 5 per cent; extragestational complications in 14 per cent; and miscellaneous or unknown in 16 per cent. The maternal mortality rate for the two-year period averaged 1 per 1000 live births. A total of 6873 Cesarean sections were performed in 1948, a rate of 4.3 per cent of all deliveries; 31 fatalities occurred, or a maternal death rate of 4 6 per 1000 births by section.

Hemorrhage was the most frequent cause of maternal death in downstate Illinois in a three-year period, 1948 to 1950, and accounted for 35 per cent of the mortality as tabulated by Newberger of the State Public Health Department (28). Of the total 237 maternal deaths in the course of 318,000 live births, toxemia was given as the cause in 26 per cent; infection in 13 per cent; embolism in 13 per cent; anesthesia in 5 per cent; and other causes in 8 per cent. The maternal mortality rate based upon a total of 237 maternal deaths (after elimination of 96 fatalities due to nonobstetric causes) averaged 0.74 per 1000 live births. Delivery by Cesarean section was involved in 73 deaths, or 43 per cent of postpartum deaths Births in the hospital averaged 94 per cent.

Coincidental Diseases.—Although 90 per cent of maternal deaths in the country at large are caused by hemorrhage, toxemia, and infection; reports of certain localities show that fatalities from these three major causes have almost disappeared. Deaths are now primarily related to diseases of the mother coincidental to pregnancy, it was pointed out by Hofmeister & Stouffer (19) of Milwaukee in a report of four maternal fatalities in more than 10,000 deliveries from 1946 to 1949. Similarly, Davis (8) cited the occurrence of eight deaths in 23,081 deliveries in Chicago from July 1, 1944 to July 1, 1950, thrombosis and embolism were the most frequent causes of death, and heart disease became relatively more important as mortality from other causes declined. In the control of hemorrhage, toxemia, and infection, a major factor has been increased hospitalization of maternity patients As Davis noted, the hospital has provided manifold safeguards; it has made available trained personnel at all times for all patients; the advances of other fields of medicine and surgery have been brought to bear in obstetrics; and the education of future obstetricians has been improved.

Anesthesia.—In a survey of maternal deaths following Cesarean section in Brooklyn from 1937 to 1950, Gordon of the Maternal Welfare Committee reported in a total of 242 fatalities that, except for infection, anesthesia was the principal factor causing death, being the chief cause in 20 per cent and definitely contributory in an additional 13 per cent In the development of the technique of Cesarean section, every modification has been designed to reduce the mortality from infection. However, the survey shows that anesthesia and hemorrhage combined are more important factors in causing death than is infection. "No greater contribution to the safety of Cesarean section could be made than the organization of a well-staffed department of anesthesiology and its integration with the department of obstetrics" (17).

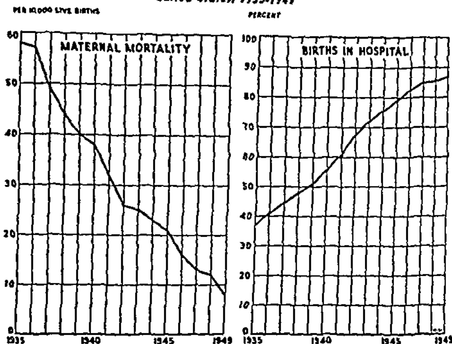


FIG. 1. Maternal mortality decreased as hospital care during labor increased. *Statistical Bulletin*, Vol. 32, 7, 1 (1951).

The Leading Cause of Death in Various Localities

Demonstration of the chief causes of maternal mortality is closely linked with the discovery of methods to prevent it. In this connection certain current reports from different localities are of special interest.

Toxemia.—Toxemia was the commonest cause of maternal death in a Southern rural area of 30 counties in which Ferguson (15) investigated 47 consecutive fatalities which were reported within 12 months in 1948. He interviewed the physicians and midwives in each case and noted that hemorrhage was second, but only half as frequent as toxemia, while pulmonary embolism outranked puerperal infections. Of 180 maternal deaths in the entire state during this period, toxemia was given as the cause in 40 per cent; hemorrhage in 22 per cent; infection in 8 per cent; and other causes in 30 per cent. Of the total births in the state, more women were delivered at home than in a hospital.

Hemorrhage.—Hemorrhage was the leading cause of maternal death in New York City during 1948 and 1949 as reported by Faison of the City Department of Health, and accounted for 20 per cent of the fatalities (14). Of the total 412 maternal deaths in the course of 315,000 live births, infec-

23 women by Dhunér (10) in Sweden. Trichloroethylene and air was given as an analgesic. In the first and second stage, when the concentration of trichloroethylene was about 0.25 per cent, arrhythmias occurred 8 times in 18 cases, during the third stage, when about 0 5 per cent trichloroethylene was given, arrhythmias occurred 13 times in 20 cases. The cardiac changes were more frequent and more severe with the higher concentration, i e. abnormal beats were more frequent and came from more foci. Among 2000 cases of obstetric analgesia, two women showed signs of transitory cardiac embarrassment.

Methadon.—A careful evaluation of methadon, a potent new synthetic analgesic, has been reported by Davis, Andros & King (9). After a single dose of 10 mg. of methadon and 0 4 to 0.5 mg scopolamine subcutaneously, in 1000 cases it was found that analgesia and amnesia were excellent in 63 per cent, moderate restlessness was noted in 22 per cent, and marked restlessness occurred in 15 per cent At delivery, low spinal anesthesia was given in 560 patients; and ethylene was administered to about 440 women. The number of primiparas and multiparas was about equal. No significant prolongation of labor was detected Failure of the babies to breathe spontaneously during the first 5 min. was noted in 15 per cent of those delivered with inhalation anesthesia, and in about 5 per cent of those delivered after low spinal anesthesia. Of the 24 babies of the series which weighed less than 2600 gm. only three failed to breathe in less than 3 min.; in the premature group, anesthesia was equally divided between ethylene and spinal. Uncorrected mortality of the babies included four intrapartum and five postnatal deaths.

N-allylnormorphine.—N-allylnormorphine, as an antidote to counteract the depressant effects of morphine upon respiration and reflexes, has recently been called to the attention of obstetricians by Eddy (13). Although the antidotal action of this morphine derivative was clearly recognized by Pohl in 1915, it had found no use in obstetrics. Recent investigations show that N-allylnormorphine also counteracts the depressant action of meperidine and methadon, but not that induced by barbiturates.

Following administration to the mother, N-allylnormorphine readily passes the placental boundary into the fetus and effectively counteracts the depression of respiration and reflexes induced by morphine, meperidine, or methadon before birth [Snyder (35), Eckenhoff, Hoffman & Dripps (12)]. A dosage of 0 5 mg of N-allylnormorphine intramuscularly in newborn infants has been found at the Boston Lying-in Hospital by Hershenson & Snyder (36), to counteract the depressant effect upon the child of 10 mg of morphine administered to the mother 1 to 3 hr. before delivery under local infiltration anesthesia It is clear that the margin of safety in the obstetric use of morphine may be greatly increased by the effective antidotal action of N-allylnormorphine to the depressant effect upon the child. In fact, in any accidental overdosage with morphine, meperidine, or methadon (16), even in adults, the evidence indicates that N-allylnormorphine affords by far the most effective treatment.

Barbiturates in preeclampsia.—Of outstanding interest is the measure-

The trend toward employment of Cesarean section has rapidly increased during the past 15 years. Colvin (6) estimates the nationwide incidence averages 2 per cent, and in large maternity centers the average is 6 per cent. Thus, it is of increasing importance to recognize the principal lethal factors involved in Cesarean section, especially one like anesthesia, the fatal effects of which may be prevented.

Medication During Labor

Spinal and inhalation anesthesia.—Regarding the margin of safety in obstetric anesthesia, Orkin & Rovenstine (29) have pointed out that in Cesarean section, the administration of spinal anesthesia because inhalation techniques are more difficult than spinal puncture, is never justified. The number of cases having neurological complications following Cesarean section with spinal anesthesia seems to be increasing. Nearly every clinic practicing or having attempted spinal anesthesia can relate at least one sudden death and many instances of relatable morbidity such as distention, thrombophlebitis, and permanent neurological disorders. In toxemia, the hypertension cannot be reduced by sympathetic block with high spinal anesthesia unless additional stress is placed upon the vascular compensatory mechanisms. In tuberculosis, spreads or reactivation occur with all types of anesthesia and with all agents; they are related to a stormy anesthesia course rather than the drug or technic. In antepartum bleeding or impending shock, spinal anesthesia is generally contraindicated. Cyclopropane is the least harmful anesthetic agent in the advent of hemorrhagic shock.

In an outline of present trends in obstetric analgesia and anesthesia, Hershenson (18) has given an authoritative appraisal of the wide range of usefulness of the various pain-relieving agents when employed by the anesthesiologist in close cooperation with the obstetrician. The length of the first stage of labor provides opportunity for preanesthetic medication of considerable variety; a prerequisite in its selection in each patient is to determine the time and type of anesthesia for delivery; for "the misuse of nonvolatile analgesic agents is more significant in the production of neonatal asphyxia than is the proper administration of inhalation anesthesia." In the use of scopolamine for amnesia during labor, Hershenson has employed apomorphine in subemetic doses, as a safe antidote to counteract the excitement often associated with scopolamine In a series of 500 patients, White (44) reported that no memory of labor was present in 87 per cent and excitement was controlled following repeated doses of scopolamine, 0.4 mg (1/150 grain), and apomorphine, 1 mg. (1/50 grain), given intramuscularly or intravenously. No injurious effect was evident in the babies. For anesthesia at the time of delivery, the wide range of effectiveness of the various inhalation agents is pointed out by Hershenson and the basis is indicated for the increasing tendency to restrict spinal anesthesia to patients with special indications.

Trichloroethylene.—Cardiac irregularities due to trichloroethylene given during labor were investigated by electrocardiographic records obtained in

Schmidt were reported also by McCall, Finch & Taylor (24). Determinations of cerebral blood flow 30 to 60 min. after 120 mg of papaverine intravenously, or 180 mg. intramuscularly, showed relief of cerebral vasoconstriction with resultant increase in cerebral blood flow and oxygen utilization by the brain; mean arterial blood pressure also was lowered. Unfavorable results following papaverine 40 mg intramuscularly in 40 preeclamptic and eclamptic patients were observed by Timonen & Schroderus (38) using other methods. Evidence of decrease in cardiac output with impairment of the peripheral circulation was noted; headache and cramps increased at times, and effects at high diastolic levels were ominous.

Levo-isomethadon.—Levo-isomethadon was found to exert a powerful influence upon the outcome of labor in rabbits following administration at the time of parturition. In observations on the birth of 550 fetuses, Snyder (33) found that following a single injection of 6 mg./kg. intramuscularly at 31 days, fetal mortality increased to 18 per cent, or almost twice that noted in uninjected controls, and labor was prolonged in 14 per cent of the animals At a total dosage level three times as great, i e., three injections of 6 mg./kg. in the course of 24 hr. further increase in stillbirths occurred, amounting to 40 per cent. In 37 per cent of the animals, labor was prolonged for a period of hours or days.

Direct observation of breathing fetuses within the unopened uterus, after laparotomy in a saline bath, revealed that fetal respiratory movements were depressed or temporarily abolished immediately after intravenous injection of 1 mg.,/kg. of levo-isomethadon into the mother.

Meperidine.—Meperidine (Demerol) was found by Snyder (34) to exert definite influence upon the outcome of labor in rabbits following administration at the time of parturition. Increase in the incidence of stillbirths and increase in the occurrence of prolonged labor afforded evidence of the effect upon the uterine expulsive mechanism. Observations on the spontaneous birth of 650 rabbit fetuses following meperidine, showed clearly that increase in the dosage increased the risk of death for the fetus during expulsion through the birth canal. Thus, following a single injection of 40 mg./kg. subcutaneously at the time of labor, 30 or 31 days, fetal mortality increased to 15 per cent, or definitely greater than that noted in uninjected controls; and labor was prolonged for a period of hours or days in 11 per cent of the animals. At a total dosage level three times as great, i e., three injections of 40 mg./kg. in the course of 24 hr further increase in stillbirths amounting to 27 per cent was noted; and in 23 per cent of the animals labor was prolonged. The rapid escape of meperidine from the maternal circulation into the fetus was demonstrable by direct observation of breathing fetuses within the unopened uterus following laparotomy in a saline bath Fetal respiratory movements were strikingly depressed or temporarily abolished immediately after intravenous injection of 5 mg./kg of meperidine into the mother. Recovery from the respiratory depression was noted, but prolongation of the period of depression was observed after repeated doses of the drug.

ment of the effects of barbiturate sedation on the brain in toxemia of pregnancy by McCall & Taylor (25). Evaluation of the effects of therapy on this organ in terms of quantitative changes in cerebral circulation and brain metabolism has been made in 32 women with toxemia by the method of Kety & Schmidt. This method involves simultaneous withdrawal of blood from the jugular vein and femoral artery over a period of 10 min. while the patient is breathing a mixture of 15 per cent nitrous oxide, 21 per cent oxygen, and 64 per cent nitrogen. Three barbiturates were studied; phenobarbital in twelve patients, amobarbital (Amytal) in eleven, and thiopental (Pentothal) in nine women. Phenobarbital (0.5 gm.) given intramuscularly, produced only slight drowsiness and did not alter any of the cerebral functions studied one hour after injection. Amobarbital (0.23 to 0.50 gm.) or thiopental (0.2 to 0.9 gm.) given intravenously until consciousness was barely lost, resulted in striking changes in the cerebral functions studied within 10 min. after injection: (*a*) highly significant depression of oxygen utilization by the brain amounting to 29 per cent depression after amobarbital and 21 per cent after thiopental; (*b*) significant lowering of cerebral blood flow amounting to a decrease of 18 per cent after amobarbital and 16 per cent after thiopental; and (*c*) mild depression of mean arterial blood pressure, about 12 mm. Hg decrease after amobarbital and 5 mm. Hg after thiopental. The elevated cerebrovascular tone that is present in typical cases of toxemia of pregnancy was not relieved by administration of any of the barbiturates studied.

In one case, in which an eclamptic convulsion occurred in the midst of blood flow determinations, it was found that the arterial oxygen level fell from 13.6 volumes per cent at 10 sec. before the convulsion, to 5.8 volumes per cent toward the end of the convulsion, and the oxygen saturation of the blood decreased from a level of about 90 per cent to lower than 40 per cent despite the administration of 85 per cent oxygen. The uptake of oxygen by the brain decreased almost 50 per cent. After the convulsion, the return to normal oxygenation of the arterial blood was gradual, requiring about 40 min. despite the breathing of 100 per cent oxygen. It is evident there is anoxic anoxia due to respiratory difficulties during the convulsion, which in turn is superimposed upon the histotoxic anoxia present during the comatose stage of eclampsia, despite the presence of a normal oxygen supply. As to medication in preeclampsia, barbiturates would be useful in so far as convulsions with their deleterious effect on the brain can be prevented with moderate doses, which produce relatively transient depression. In the presence of convulsions, there is evidence that the use of large and continued doses of barbiturate which add to the depression of the postconvulsive state are contraindicated, especially from the standpoint of possible permanent cerebral damage. Intravenously administered barbiturate is particularly pernicious in this respect.

Papaverine in Preeclampsia.—Favorable cerebral effects of papaverine in 10 women with toxemia of pregnancy studied by the method of Kety &

Indeed, in several states in which hospital care is minimal the neonatal death rate was above 30 per 1000 live births in contrast to the national average of 22.

From even a brief survey of the magnitude of the mortality associated with birth it is evident that the highest peak of mortality during the period of gestation and early infancy—in fact during the entire life span—coincides with the day of birth From the standpoint of mortality, escape from the uterine environment is the most dangerous experience of life. The answer to the question of what types of injury occur during labor and are chiefly responsible for intranatal or postnatal fatalities has been sought from a variety of sources including autopsies, clinical reports, and experimental analysis. One conclusion from such inquiry stands out preeminently; the fetal respiratory system is the site of greatest vulnerability to injury that proves fatal during labor or following it. Thus, it is easy to understand that the respiratory injuries occurring during labor, asphyxia neonatorum, congenital pneumonia due to aspiration of contaminated amniotic fluid, and atelectasis, are of utmost interest and have prompted numerous investigations, a few of which may be cited.

Autopsies.—Pulmonary lesions subsequent to asphyxia or aspiration were the leading cause of fetal and neonatal death found by Labate & Dickson (21) in a series of 1225 autopsies obtained in the course of about 25,000 births at Bellevue Hospital, New York during 15 years ending in 1948. More than half of the deaths of viable babies were related to pulmonary lesions or intrauterine death resulting in maceration. In a group of 123 full term babies autopsied during 1943 to 1948, pulmonary lesions were noted as the cause of death in 55 per cent; birth trauma in 14 per cent; maceration in 13 per cent; and other causes in 18 per cent. The types of pulmonary changes in the 68 babies dying with lung abnormalities included massive aspiration of amniotic fluid in 50 cases; pneumonia in 8 babies; and massive hemorrhage of the lungs in 10 cases. Despite administration of penicillin during labor with premature rupture of the membranes, and treatment of the baby following delivery, no reduction of the incidence of congential pneumonia was noted.

In the group of 101 viable premature babies autopsied during 1943 to 1948, pulmonary lesions were found as the cause of death in 30 per cent; maceration in 24 per cent; primary prematurity in 19 per cent; congenital anomalies in 8 per cent; birth trauma in 6 per cent; and other causes in 13 per cent. Intrauterine asphyxia was held responsible for more than 90 per cent of the pulmonary lesions in the premature infants; of the 31 babies with lung abnormalities, there was massive aspiration of amniotic fluid in 19; pneumonia in 6; hyaline membrane in 3, and hemorrhage of the lungs in 3.

Autopsies upon 8905 babies dying after birth in Chicago from 1936 to 1949 showed that respiratory injuries were by far the leading cause of death (4). About half of the deaths were attributed to "abnormal pulmonary ventilation" and anoxia; and about one-tenth to pneumonia. Despite the

Anemia.—The duration of labor was increased 20 per cent in women with anemia, i.e., less than 11 gm. of hemoglobin per 100 cc. of blood, at the time of spontaneous delivery under standardized conditions (39). In a series of 1000 deliveries in Georgia, of which one-third were in women with anemia, Traylor & Torpin found the duration of labor in 77 anemic primiparas was increased to 18 hr. in contrast to 15 hr. in the normal controls; and in 227 anemic multiparas labor averaged 12 hr. instead of 10 hr. as in normal patients. Impairment of the oxygen-carrying capacity of the blood also implies other deficiencies in the nutrition of the uterus during labor.

Safety.—After review of the powerful anesthetic agents now available and the precautions essential for their use, Knight (20) concluded that

> in obstetrics the main obstacle to complete pain control is an economic one. Certainly we have the knowledge and the equipment to accomplish this but to do so would require professional attendance upon the patient many hours for pain relief and for the maintenance of good physiology. A short-cut to pain relief has too often been accompanied by bad physiology with disastrous results. Obstetrical pain relief has therefore been classed as dangerous. People are as unprepared or unwilling to pay the price of long attendance to avoid the danger and still to have pain relief.

Stillbirth and Neonatal Death

From the standpoint of mortality, the hazards of birth are, of course, far greater for the child than for the mother. How great the risk is for the child is set forth in the publication by the Census Bureau in 1952 of an analysis of infant mortality in the United States in 1949; for every 100 live births, more than four babies are born dead or die soon afterwards This current rate, it was pointed out, is the lowest incidence of fetal and neonatal (*infants* dying within 28 days) deaths hitherto reported in the nation, the stillbirths were 19 8 per 1000 live births; and infants dying in the first month were 21.4 per 1000. Thus, in the course of 3,500,000 live births in 1949 more than 140,000 babies succumbed during birth or shortly afterwards (42).

[illegible] fetal and neonatal mortality, the [illegible]

of life than it has among the newborn. For instance, since 1915, the mortality rates for infants under one day have declined only one-half as much as in the case of infants in the age group three to six days, or 30 and 60 per cent respectively. *Consequently, deaths in early infancy have come to form* an increasing proportion of total infant mortality. Since 1915, the proportion of infant deaths occurring under one week of age has nearly doubled, increasing from 30 to 58 per cent This difference in the trend by age reflects greater progress made in the control of the diseases which have their origin in the postnatal environment than in the control of abnormal conditions or influences which exist at or prior to birth

Regarding hospital care, it was noted that nearly half a million babies were born at home in 1949, and about 170,000 were delivered by midwives.

is to be made, then all primiparas should be treated and all multiparas who have been in labor more than 12 hr. or who have anemia or have lost more than 500 cc. of blood, or who have been operated on or have retained fetal membranes In practice it was found difficult to realize such differentiation The question is raised as to what results can be obtained by similar use of relatively small prophylactic doses of antibiotics such as penicillin and aureomycin, which are readily transmitted to the fetus.

Many more babies survived and fewer mothers showed "infection amniotique" following administration of 4'-Sulfamyl-2,4-diaminoazobenzene hydrochloride (Prontosil), 2 gm daily during labor in the Baudelocque Clinic, Paris. Bret (3) reported that only one-third as many babies died and only one-fourth as many women showed puerperal infection in the series of treated cases as compared with women not treated, in the course of a total of 25,000 deliveries However, it was noted that sulfonamide therapy did not increase the survival rate of fetuses after amniotic infection was established, but indirectly, by reduction of the number of amniotic infections, protection of the child was achieved.

Increased hazard for the child, following large doses of sulfonamides administered during labor, may be related to the diminished rate of elimination of the drug from the blood of the fetus or newborn in contrast to that of the mother Thus in a series of 150 rabbits following 0.5 mg./kg. of sulfadiazine subcutaneously, Snyder found that the blood was negative in adults in less than 12 hr. while in premature animals of 30 days the blood contained 6 mg./100 cc. 24 hr. after injection (32). At 18 hr., the blood level in fullterm newborn animals of 32 days was 14 mg.; in suckling infants of one week it was 5 mg ; and at two weeks or older the blood was negative. Much higher concentration of sulfadiazine was noted in the blood of the newborn than in that of adults despite uniform dosage. At 1 hr following injection, the blood level in adults averaged 22 mg., while in prematures it was twice as great, averaging 47 mg In the newborn at term it was 41 mg ; in suckling animals at one week it was 33 mg , and at 4 weeks was 27 mg. At 6 hr. after injection, the blood level in the newborn averaged 35 mg in contrast to 7 mg in adults.

Permanent injury of the central nervous system.—A wide range of abnormalities of the central nervous system, apart from those of hereditary origin, have been noted during infancy and childhood, and, while it has long been evident that the time of origin of the injuries dated back to the time of birth, their etiology has been difficult to establish By far the greatest hazard for the child in the course of birth is respiratory failure. Fatal asphyxia during labor, however, commonly leaves little or no imprint after death Autopsy findings are essentially negative. What permanent lesions result following sublethal degrees of anoxia is the subject of the following investigation.

In an analysis of the postmortem findings in the brains of mentally deficient, spastic, or epileptic patients, Courville (7) pointed out that cerebral anoxia is capable of producing a considerable variety of structural changes

introduction of sulfonamide drugs and the antibiotics, neonatal mortality rates from infection showed no decrease.

In Chicago during 1951, 75 per cent of all infant deaths occurred during the first month; 88 per cent of the deaths during the first month occurred *during the first week, and 50 per cent of the deaths in the first week occurred* during the first day. Although 8 per cent of all births in 1951 were premature, 70 per cent of all the neonatal deaths were in premature infants. At full term, neonatal deaths were 6 per 1000 live births.

Prevention of stillbirth.—A striking decrease in the number of babies dying during labor, a result achieved when sulfamerazine was administered to the mother in small doses, was reported by von Friesen in Stockholm, Sweden (43). Intrauterine mortality was only half as great following sulfamerazine prophylaxis as occurred in untreated cases of a total series of 5000 babies which were delivered in the same hospital during the same period of time. Following prophylactic sulfamerazine in the course of 2235 births there were only 15 fetal deaths during labor in contrast to 35 intranatal fatalities among 2259 births in controls which were untreated Just as many fetuses in both groups died before labor, i e., before any prophylactic treatment could be given; thus 20 fetal deaths before labor occurred in the treated cases and 18 in the untreated group. Neonatal mortality during the first week of life revealed no effect by sulfamerazine therapy; there were 39 deaths among treated cases, and 40 deaths in the controls which were untreated. Von Friesen pointed out that the prophylaxis effected a decrease in fetal deaths during labor, probably through lessening of the frequency and degree of intrauterine infection. Thus, there is evidence that treatment must be started before the intrauterine infection manifests itself. With infection already well established, the number of fatalities, despite prophylaxis, was just as great as ever.

Administration of sulfamerazine was begun as soon as possible during labor; 1 gm. was given orally, followed by 0.5 gm twice daily up to and including the fourth day after delivery; the total dosage received by each patient was 5 8 gm. in 4 9 days Blood samples showed that sulfamerazine averaged 1.8 mg per 100 cc in the maternal blood during labor, and 1 4 in fetal blood. In amniotic fluid during the first 6 hr , sulfamerazine averaged 0 4 mg. per 100 cc. and subsequently reached 1.0 mg. After delivery, the maternal blood level rose rapidly to 3.0 mg. per 100 cc The frequency of puerperal infection was reduced by half, and pyelitis was decreased 80 per cent. In view of the low dosage and brief duration of the sulfonamide therapy, no complications such as renal impairment, anemia, or toxic effects upon the fetus, were anticipated and no complications were observed. Since no obvious cause of puerperal infection was found in about 20 per cent of the cases; and since intrauterine infection during labor produces, at first, no clinical symptoms and is one of the causes of fetal death during labor, von Friesen concluded that prophylactic treatment must be started before symptoms appear and recommended its use for all women in labor If any differentiation

livery by Cesarean section, 10 showed hyaline membranes. No hyaline membranes were noted in 187 stillborn babies or in 34 infants surviving less than 1 hr.

Regarding the etiology of hyaline membranes, Miller, Behrle & Gibson (27) noted that pulmonary edema was invariably encountered in the lungs of newborn infants in which hyaline membranes were present. By means of bilateral vagotomy in 20 adult rabbits, pulmonary edema was produced in every animal, resulting in death 3 to 25 hr. after operation. Pulmonary hyaline membranes similar in appearance to those seen in newborn infants were found in 13 of the 20 rabbits The time of appearance of these membranes following operation in the rabbits closely approximated the time of appearance of the membranes seen in the lungs of newborn infants in respect to the time of birth.

Prevention—Calkins (5) pointed out how to decrease fetal mortality in a review of the causes of death observed in the antepartum, intrapartum, and neonatal periods in 5600 consecutive births, with the occurrence of 154 deaths. (*a*) Premature labor may be reduced by prenatal treatment of toxemia and syphilis, (*b*) fetal injury during labor related to analgesia, anesthesia, and operative delivery may be clarified by additional autopsies, thus facilitating the prevention of fetal death.

Fetal mortality in 1834 Cesarean sections from 1933 to 1949 at New York Hospital was tabulated by Landesman (23) according to the indications which prompted operative delivery. While fetal mortality in Cesarean section was 2 5 times higher than in the clinic material, this relatively high fetal mortality was related to the indication for the operation, rather than the procedure itself. Cesarean section for cephalopelvic disproportion was of no more risk to the baby than spontaneous vertex delivery, the mortality being 0.4 per cent in 534 sections for this indication Suggestions for reduction of fetal mortality associated with Cesarean section include: (*a*) local anesthesia, especially with premature babies; (*b*) high concentrations of oxygen during and after section; and (*c*) a readily available premature nursery.

Elevation of the placenta to facilitate blood flow toward the infant at the time of delivery by Cesarean section was found by Landau, *et al* (22) to reduce the incidence of dyspnea, cyanosis, and shock; indeed, in 87 babies thus treated, none showed signs of shock such as frequently was noted after immediate clamping of the cord.

After spontaneous birth, Windle's (45) measurements showed that when clamping of the cord is delayed until after separation of the placenta, the baby receives about 100 cc. more blood than when the cord is clamped immediately, and even at the time cord pulsations cease, less than half this amount has reached the child.

In babies delivered by Ceasarean section, the effect of stripping or milking of the umbilical cord to propel blood into the child, in contrast to the effect of immediate clamping of the cord, was investigated by Siddall,

in the brain, including the lesions which are characteristic of these so-called degenerative diseases. As to localization of asphyxial injury, necrosis of some parts of the corpus striatum is commonly found. Certain focal effects which follow antenatal or neonatal anoxia, can be accounted for only on the basis of the action of anoxia on the function and structure of blood vessels. The reasons it has taken a century or more to determine that such a kaleidoscopic variety of organic cerebral states may result from anoxia at birth is Courville explains: (a) that medical science has been very slow to distinguish between the mechanical effects of trauma at birth on the one hand, and the chemical and physiologic effects of anoxia which so often accompany birth injuries on the other; (b) the pathology of anoxia is a relatively recent product of neuropathology. Indeed, the total concept of diffuse loss of nerve cells in the cerebral cortex and corpus striatum, the sclerosing effects of focal necrosis, the late residuals of anoxia in the form of demyelination and cyst formation, and the secondary changes consequent to the occlusion of vessels following asphyxia, have not been widely appreciated. As to the time of occurrence of the anoxia, Courville's observations indicate that many of the injuries originate in anoxia occurring before birth.

Fetal respiration.—Abnormal development of the pulmonary vascular system was noted by Milles & Dorsey (26) in two fullterm infants which were born alive but made only futile attempts to breathe. Autopsy revealed absence of the trachea in one and absence of the diaphragm in the other. Thus, normal expansion of the lungs was impossible before birth as well as afterwards. The ductus arteriosus was so large that its diameter was twice that of the aortic isthmus instead of being the same size or smaller as in normal infants. As the authors point out, this evidence that the normal development of the pulmonary vascular system before birth depends upon the expansion of the fetal lungs, illustrates the essential physiologic nature of intrauterine respiratory movements.

Intrauterine pneumonia.—Intrauterine pneumonia was found in about one-third of the stillborn babies in which the lungs were examined microscopically by Ahvenainen at Helsinki during a period of two years (1). In the series of 45 stillborn babies, which included 32 at term and 13 prematures, pneumonia was observed in 28 per cent of the fullterm stillbirths, and in 38 per cent of the premature fetuses. Clinically, death was attributed in the majority of cases to fetal asphyxia.

Hyaline membrane.—In the lungs of infants dying within a few hours or days after birth, Blystad, Landing & Smith (2) observed a high incidence of hyaline membranes upon microscopic examination. In infants surviving 1 to 24 hr., hyaline membranes were found in 47 per cent of 127 babies; in 40 per cent of 65 babies dying on the second day, and in 10 per cent of 10 babies surviving until the fifth day. In premature infants, hyaline membranes were found twice as often as in term babies, the incidence being 44 per cent and 22 per cent respectively in 280 infants living five days or less, half of which were premature Of 15 fullterm infants dying within 5 days after de-

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Crissen & Knapp (31) in 100 consecutive newborn infants in which determinations were made of the hemoglobin concentration and erythrocyte count of the blood. In 50 babies, in which the cord was ligated immediately after delivery, the hemoglobin averaged 15.9 gm. per 100 cc. of blood, while in a second group of 50 infants in which stripping of the cord was carried out, the hemoglobin averaged 17.2 gm.; similarly, an increase in erythrocytes which averaged 5.35 million after stripping of the cord was noted in contrast to 4.76 million in the control group.

In placentas obtained at delivery, the pathway of the fetal blood was traced by Romney & Reid after injection of India ink or vinyl acetate (30). The fetal capillary network though extensive, was found to be short in linear magnitude—an adaptation which may contribute to rapid venous return.

TROPICAL DISEASES[1]

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INTRODUCTION

Tropical Medicine is an anomalous matrix of knowledge concerning unrelated diseases, many of which are not restricted to the torrid zone. The subject matter grew out of tribulations encountered in the tropics by economic projects launched in undeveloped areas during the past 100 years. Hyperendemic malaria, trypanosomiasis, dysentery, yellow fever, and other diseases were costly, frustrating obstacles to economic and political evolution of primitive areas. To meet this challenge, centers were established in London, Liverpool, Amsterdam, and Hamburg for the purpose of training experts to study those diseases which were the greatest problems in the tropics, and to develop effective means of control. As a result of this enterprise, a large body of information was obtained for use in the tropics and elsewhere.

The only exclusively tropical diseases are those characterized by etiological agents having obligatory intermediate or definitive hosts whose geographical distribution is restricted to the tropics However, vectors of such major diseases as malaria, yellow fever, and plague are not restricted to the tropics; they have been or still are important or potential problems in temperate areas. Furthermore, it must be noted that those infectious diseases which are fostered by poor sanitation, including cholera, the typhoid fevers, bacillary dysenteries, and amebiasis, are still among the more acute problems encountered in the tropics, and these conditions are still either endemic or are potential threats in large areas of the temperate zones Such diseases recede before the advance of sanitized urbanization, but they continue to smoulder and are likely to flare up when and where there is a break in sanitation practice, whether it be in Madagascar, Dublin, or Long Island.

The area of medical sciences encompassed in the term "Tropical Diseases" precludes an encyclopedic review of recent advances in pertinent knowledge, so we shall consider only selected phases of two of the "tropical" diseases of widest interest, malaria and amebiasis

MALARIA

Despite progress in malaria control during the past 30 years, means of eradication have proved elusive and malaria is still the greatest single threat to human life in many parts of the world (1). However, prospects for true eradication of malaria, on a regional or even a national scale, have been materially brightened by recently increased knowledge of malaria parasites and their behavior in pathogenesis and immunity, by development of highly

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in canaries, including large nonpigmented schizonts in reticulo-endothelial cells [Raffaele (21, 22, 23)]. The pre-erythrocytic schizogony of *P. gallinaceum* in reticulo-endothelial (R.-E.) cells of brain capillaries in the fowl was described by James & Tate (24, 25) who introduced the designation "exo-erythrocytic" (E.-E) forms. Studies on other species quickly established the general occurrence of exo-erythrocytic schizogony in avian malaria [Porter & Huff (26)]. Huff & Coulston (27) produced a full description of the development of *P. gallinaceum*, from sporozoite to intraerythrocytic trophozoite, and Huff, Coulston & Cantrell (28) introduced the term 'cryptozoite' to designate the first generation E.-E. form derived from a sporozoite. The merozoite progeny of cryptozoites may enter red blood cells, or alternatively may continue the tissue phase of schizogony as "metacryptozoites" In *P. gallinaceum* infection, onset of parasitemia coincides with the peak of metacryptozoic development and outpouring of merozoites into the blood. In man, E.-E. forms apparently do not result from blood induced malaria, but in avian malaria merozoites of erythrocytic origin may parasitize endothelial cells (29, 30).

Identification of exo-erythrocytic forms in human and simian malaria has been more difficult. The first conclusive demonstration of E.-E. forms in primates was by Shortt, Garnham & Malamos (31) who found large nonpigmented pre-erythrocytic schizonts of *Plasmodium cynomolgi* in liver cells of a monkey seven days after inoculation with sporozoites from more than 500 mosquitoes. This observation was immediately confirmed by Hawking (32). Shortt *et al.* (33) extended their procedure to a human volunteer and demonstrated pre-erythrocytic schizonts of *P. vivax* in parenchyma cells of liver tissue obtained by biopsy. The descriptions of pre-erythrocytic *P. cynomolgi* and *P. vivax* were subsequently extended by Shortt & Garnham (34). The development of *P. cynomolgi* was observed from the fifth to tenth day after infection. The earliest forms seen in liver cells were oval multinucleated parasites, about 10 μ in diameter. The size of the parasite and number of nuclear granules increased over the five-day period of observation. Larger forms were lobose, contained one or more prominent vacuoles, and had a smooth contour suggesting a surrounding pellicle. The seventh day form was about 31 μ in longest diameter and contained approximately 1,000 nuclei. Eighth-day schizonts showed early signs of segmentation, followed by development of merozoites on the ninth and tenth days. During development of the schizont there was no evidence of cellular reaction, but when a mature shizont ruptured there was immediate infiltration of the area by phagocytic cells.

The description of *P. vivax* is less complete (34) The earliest (sixth day) form was about 42 μ in diameter, contained some 800 chromatin masses, and showed signs of segmentation of the cytoplasm The second form described (seventh day) was a ruptured schizont showing liberation of merozoites These forms resembled those of *P. cynomolgi* in the monkey, but apparently developed more rapidly. The volunteer host did not subse-

effective suppressive and curative drugs, and by development of more effective agents and methods of vector control.

The vast literature on malaria has been compiled by Boyd (2), and an important review of recent research in malaria comprises the first 1951 issue of the *British Medical Bulletin* (3).

Life History of Malaria Parasites in Man

The erythrocytic phase—The early descriptions of schizogony were essentially complete. Recent refinements include demonstration that *Plasmodium vivax* has a marked predilection for reticulocytes (4), whereas *Plasmodium malariae* rarely infects immature cells and *Plasmodium falciparum* affects mature and immature blood cells indiscriminately (5). Research on erythrocytic plasmodia has been concerned mostly with study of their physiology and metabolism, recently reviewed by Fulton (6). Most of the data have been obtained using concentrates of *Plasmodium gallinaceum* in chicken blood, and *Plasmodium knowlesi* in monkey blood. Geiman and associates (7 to 10) elaborated procedures which permitted rapid multiplication of *P. knowlesi* schizonts as well as important observations on metabolism, nutrient requirements, and the action of schizontocidal drugs. Trager (11) has found it possible to obtain multiplication of erythrocytic plasmodia outside of cells. That obligatory erythrotropism is a result of metabolic dependence upon hemoglobin is suggested by the observation that quinacrine prevents the formation of malaria pigment (hematin) in susceptible parasites [Mackerras & Ercole (12, 13)]. The fact that quinacrine inhibits pigment formation in *P. falciparum* gametocytes, but does not reduce their infectivity for mosquitoes, indicates that these gametocytes are metabolically independent of hemoglobin (13), as are the stages in the mosquito and pre-erythrocytic forms in the vertebrate host.

The use of malaria for treatment of paresis led to study of induced malaria under controlled conditions, and resulting contributions have been reviewed by Covell & Nicol (14) Particularly significant has been recognition that morphologically indistinguishable strains of vivax and falciparum malaria may differ widely in the clinical pattern of the disease produced in degree of cross immunization, and in susceptibility to drugs

Induced malaria in volunteers has permitted rapid critical evaluation of new suppressive and curative drugs (15, 16, 17).

Grassi (18) suspected that sporozoites underwent development in the tissues before invasion of erythrocytes occurred, but Schaudinn's (19) inaccurate account of their penetration into red blood cells prevailed until James (20) pointed out that clinical experience in malaria was incompatible with the concept of a purely erythrocytic cycle in man James suggested that the ineffectiveness of quinine for causal prophylaxis was due to sporozoites finding a hiding place in the connective tissue or reticulo-endothelial cells instead of immediately attacking erythrocytes. Support for James's concept came from elucidation of the development of *Plasmodium elongatum*

was found in one human case, and two giant schizonts were found in the monkey liver. These forms appeared to be in reticulo-endothelial cells and parasites were not found in liver parenchyma cells as described by Shortt & Garnham (34).

The role of exo-erythrocytic development in determining the tendency to clinical relapse is readily inferred. Shortt & Garnham (42) have attributed the relapse pattern of cynomolgi and vivax malaria to persistence of the tissue cycle of development in the liver (secondary pre-erythrocytic forms as observed for *P. cynomolgi*). Actually, in vivax malaria, persistent developmental forms associated with an established clinical relapse pattern have *not been observed in liver parenchyma cells*. The available evidence, without invalidating the account of pre-erythrocytic development in liver cells following massive infection, suggests that relapses may arise from E.-E. forms in reticulo-endothelial cells in various sites including the liver and bone marrow.

The difference between recrudescences resulting from multiplication of erythrocytic parasites which have been continuously present in the blood, and the relapse phenomenon which is from reinfection of blood cells by merozoites liberated from persistent E.-E forms, has been emphasized by Garnham (43). He believes that in relapsing *P. vivax* and *Plasmodium malariae* infections, exo-erythrocytic multiplication is probably continuous, but as a rule escaping merozoites are destroyed by an immunity mechanism; periodic reduction of this immunity leads to relapse. In *P falciparum* infection it is believed that E.-E development does not persist beyond the initial pre-erythrocytic phase, hence true relapses of this infection do not occur. It should be noted that recrudescences are likely to follow inadequate treatment in all types of malaria.

Before considering the chapter on the exo-erythrocytic development of the plasmodia of man as closed, it should be noted that Porter & Huff (26) cited numerous instances of strains of bird malaria where E.-E. schizogony could not be demonstrated, or was transient after passage through mosquitoes, although other strains of the same species regularly multiplied in the tissues The possibility that analogous differences in cyclical behavior may be charactersitic of some strains of human malaria parasites should not be excluded at this stage of development of our knowledge. A comparison of the exo-erythrocytic development of different strains is clearly desirable, and tissues other than liver should be carefully examined after massive experimental infection.

Pathogenesis of Malaria

The pathologic anatomy of malaria has been ably reviewed by Clark & Tomlinson (44). The physiologic pathology of malaria has been summarized by Fulton & Maegraith (45), who should be consulted for details Simultaneous schizogony during a malarial paroxysm destroys enormous numbers of erythrocytes, and protein, pigment, and salts, especially potassium, as well as other components of ruptured red cells, are set free in the plasma.

quently develop patent malaria as expected, *possibly due to residual immunity* from therapeutic malaria induced by means of the same strain of *P. vivax* twenty-two and one-half months earlier.

Coulston (35) *has found* pre-erythrocytic forms of *P. cynomolgi* in reticulo-endothelial cells as well as in parenchymatous cells of the liver of sporozoite infected monkeys. Control liver tissue from non-infected monkeys showed platelet thrombi which were indistinguishable from suspected mature schizonts in infected animals, indicating that such artifacts are not uncommon and may readily be mistaken for parasistes.

The pre-erythrocytic development of *P. falciparum* has been described by Shortt *et al* (36, 37). As in the earlier experiment, the parasites were found in Giemsa-stained sections of pieces of liver obtained by laparotomy. The volunteer was prepared by massive infection with sporozoites on three successive days so that biopsy on the fourth day after the last infection could be expected to show *parasites representing the fourth, fifth, and sixth* day of development. All pre-erythrocytic parasites found were said to be in liver parenchyma cells. The earliest forms found were oval, multinucleated *parasites with a tendency to produce lobose projections. Rapid growth* and nuclear division led to formation of large irregularly lobose schizonts, up to 60 μ, longest diameter, which segmented into approximately 40,000 minute merozoites. The pre-erythrocytic development of *P. falciparum* was more rapid than that of *P. vivax* and a larger number of merozoites was produced by the sixth day. Erythrocytic forms of *P. falciparum* appeared in the blood on the seventh day after the first exposure to mosquitoes. The early maturation and rupture of the pre-erythrocytic schizonts were confirmed when a second volunteer, who had been injected intravenously with blood taken from the infected volunteer 135 hr. after initial exposure, developed parasitemia eight days after transfusion.

Huff (38) has questioned the malarial nature of some of the bodies described by Shortt and his colleagues as part of the developmental cycle of human and simian plasmodia. However, recognizing the difficulty of distinguishing between ruptured schizonts and platelet thrombi, it is clear that pre-erythrocytic stages of development of *P. vivax* and *P. falciparum* have been observed in sections of liver The thesis that exo-erythrocytic development of malaria parasites in humans is restricted to liver parenchyma cells is more questionable. During the past decade there have been at least 30

the lack of pigment is characteristic of exo-erythrocytic parasites.

Less questionable is the report by Telcharov & Todorowa (41) who studied *biopsy specimens* of liver from 45 cases of *P. vivax* malaria, and 412 serial sections of an infected monkey's liver A solitary giant schizont (42 μ)

or latent stage of infection provoked severe recrudescences. These effects were attributed to a depletion of tissue macrophages. Corticotropin (ACTH) administered to three patients with induced vivax malaria resulted in higher parasite counts, shorter duration of fever, and no change in periodicity or height of temperature, when compared with seven control patients [Kass *et al.* (53)]. These reports suggest that cortisone or ACTH should be used with caution for treatment of patients with a history of malaria.

The community aspects of immunity to malaria are extremely important. Precise information is lacking as to the cost in deaths of acquiring group immunity and the resultant status of a reservoir of infection. Macdonald (54), in discussing the attitude of certain authorities who hold that group immunity makes malaria control measures unnecessary or even undesirable in some cases, has pointed out that malaria control, in a typical hyperendemic area such as the palteau of Indo-China, was followed by a decrease in gross mortality rate of about 40 per cent.

Clinical Picture and Diagnosis

Clinical picture—For the purposes of this review there is nothing to be gained by repeating a description of the classical presentation of the four types of human malaria [Covell (55)]. However, the fact remains that typical recurrent benign tertian (vivax) malaria is too often unrecognized in former members of the armed forces who served in malarious areas, or tourists who have been attracted to some of the more picturesque but less sanitized parts of the world Recent military experience indicates that the rate of suppressed infection in returnees from Korea is very high (56), and although most of the relapses have occurred while infected personnel could receive proper diagnosis and care, some delayed break-throughs can be anticipated in discharged individuals who will patronize their family physicians in preference to the medical services offered by the Veterans' Administration.

Alving *et al* (56) recently pointed out that temperate zone vivax malaria and tropical zone vivax malaria differ chiefly in the relative length of the interval between the primary attack and the first relapse. The temperate zone vivax has a long latent interval of six to nine months, so that persons infected during the summer months, while taking suppressive drugs, may show no signs of infection until the following spring or summer if they are no longer under conditions requiring suppressive prophylactic medication. As would be expected by virtue of Korea's temperate climate, Korean malaria is of the vivax type and behaves much like the temperate St. Elizabeth strain in the United States (57).

Damage to the kidneys is a more or less constant feature which is sometimes overlooked in chronic malaria A type of nephrosis has been described as frequently complicating chronic *P. malariae* infections (2), but Gairdner (58) has used induced vivax malaria for treatment of nephrosis in children. Nephritis resulting from either chronic vivax or falciparum malaria is said

During a series of paroxysms there is an early absolute decrease in plasma albumin and a somewhat later increase in globulin; total plasma protein is decreased. The sharp drop in blood sugar level, which occurs as the temperature rises, has been related to changes in the liver and adrenal glands, with concurrent effects on kidney function. The peak levels of plasma potassium, attained just at the onset of the chill, are in excess of the potassium estimated to be released by the destroyed erythrocytes, hence potassium must be mobilized from other cells, as occurs in shock. It is noteworthy that the onset of rigor and rise in plasma potassium can be completely inhibited by intravenous injection of calcium chloride. Hepatic changes leading to centrilobular necrosis have been attributed to anoxemia induced by changes in vascular dynamics occurring as part of the shock syndrome [Maegraith, Jones & Andrews (46)]. The changes which occur in the adrenals in rapidly fatal cases of malaria (44) are of the type observed in shock of corresponding duration. In chronic malaria, symptoms such as asthenia, lowered arterial pressure, and bronzing of the skin suggest adrenal insufficiency. Zwemer, Sims & Coggeshall (47) attributed changes of potassium levels to adrenal disturbance and suggested that adrenal cortex preparations be used in treatment.

In blackwater fever there is a decrease in normal plasma inhibitor of cytolysins, so that the balance between normal tissue and plasma lysin and inhibitor is shifted in favor of excessive lytic activity [Maegraith, Martin & Findlay (48); Ponder (49)] There is also evidence that changes have occurred in the lipoprotein complex of the erythrocyte cell membrane, rendering it more susceptible to hemolysis (50).

Immunity in Malaria

Varying degrees of immunity result from either blood induced or sporozoite induced malaria The basic mechanism is phagocytosis by tissue macrophages but humoral factors play an important role in enhancing this phagocytic activity Acquired immunity to malaria is not permanent but it may persist from a few months to several years. The duration of immunity is determined by persistence of residual infection and decreases rapidly after complete cure, hence it is essentially resistance to super-infection (premunition). There is no cross-immunity between species of malaria parasites of man, and even strains of the same species may show little cross immunizing properties. The mechanisms of acquired immunity are operative against the erythrocytic phase in controlling parasitemia, but show very little capacity for preventing the establishment of homologous sporozoite induced exoerythrocytic infection in birds or monkeys The reader should consult the review by Taliaferro (51).

The tissue defenses can be effectively depressed by the action of cortisone Repetitive doses of 10 mg /kg of cortisone administered to monkeys infected with *P. cynomolgi* during the primary attack produced marked intensification of the parasitemia. Cortisone administered during the chronic

Specific chemotherapy—The specific chemotherapeutic management of malaria has been a very complex problem. The difficulties encountered are largely related to the complex etiology involving developmental phases which differ in susceptibility to a given drug Varied susceptibility of species and strains of *Plasmodium* to drugs has been a problem further complicated by acquired drug resistance.

Usefulness of an antimalarial drug depends upon the degree to which it possesses the following attributes: (*a*) ability to produce rapid clinical control of all types of acute malaria, with suppression of pyrexia and disappearance of parasites from the blood; (*b*) ability to produce a radical cure; (*c*) ability to act as a causal prophylactic, with direct lethal effect on sporozoites or pre-erythrocytic forms, and (*d*) sufficient lack of toxicity at effective dosage when given by mouth to permit wide distribution in a community with a minimum requirement for medical supervision of medication If not effective against exo-erythrocytic forms, the suppressive drug of choice must offer the alternative possibility of an effective plasma concentration being maintained, without harm to the patient, for a sufficient period of time to permit the tissue phase of the life cycle to be exhausted or an effective degree of immunity to develop.

Suppressive antimalarial drugs are selectively active against the erythrocytic cycle. They are capable of controlling paroxysmal attacks of malaria, but they do not prevent the establishment of pre-erythrocytic infection, and when used for a therapeutic course of medication will not prevent relapses arising from persistent secondary tissue stages. Adequate dosage of a drug which is classed as suppressive against vivax malaria is usually curative in the treatment of falciparum infections, hence the conventional distinction between suppressive and curative activity of drugs is not applicable to falciparum malaria. It should also be pointed out that, in children, the sequence of paroxysmal relapses of untreated vivax malaria is usually arrested by the development of some immunity, and proper management of suppressive medication of partially immune subjects may result in termination of the relapse pattern of vivax malaria Antimalarial drugs have also been classified as "schizonticides" and "gametocides," but such a distinction has no therapeutic significance because gametocytes do not enter significantly into the pathogenesis of malaria. The properties of the various antimalarial drugs, available or of special interest, may now be reviewed with respect to the desired properties outlined above.

Quinine—Quinine is 6-methoxy-*a*-(5-vinyl-2-quinuclidyl)-4-quinolinemethanol, available only as the derivative of cinchona bark Quinine is still used in areas where economic factors restrict the use of more effective synthetic antimalarials. Orally administered quinine sulfate or hydrochloride is absorbed rapidly and can be demonstrated in the blood within 15 minutes, but it undergoes metabolic degradation and excretion so rapidly that maintenance of an effective plasma concentration is difficult [Chen & Geiling (65); Pullman *et al.* (66)] Certain strains of *P. vivax* require much higher

to be so common in Tunisia that the physician should first think of malaria when he sees a patient with nephritis, edema, anemia, and splenomegaly [Corcos & Cittanova (59)]. There is rarely any cardiovascular involvement associated with malarial nephritis.

Diagnosis.—Diagnosis of malaria is never certain except when the causative parasites have been demonstrated microscopically. In malarious areas, or in the case of discharged veterans and persons with a history of having visited a malarious area within a year, examination of a blood smear should be a routine procedure. Hyperchromic anemia may be severe. A suggestive sign is enlargement and tenderness of the spleen, and the liver may be palpable and tender also. Splenomegaly and hepatomegaly are characteristic of chronic malaria in hyperendemic areas.

Diagnosis of malaria may be greatly facilitated by examination of fluid obtained from scarification of the skin [Van Den Berghe & Chardome (60)]. A site in the middle of the scapular region is cut superficially so that there is little bleeding. The scarified area is squeezed between the thumbs and forefingers to provide dermal capillary blood which is spread as a thick or thin film, air dried, stained and examined in the usual ways. All four species of malaria parasites, both as schizonts and gametocytes, are easily demonstrated. If the increased accuracy (98 to 99 per cent) is confirmed the procedure will undoubtedly become widely used for both diagnostic and survey purposes.

Treatment of Malaria

Acute malaria requiring urgent symptomatic treatment is almost invariably of the falciparum type. The algid form presents the picture of shock [Kean & Taylor (61)] and should be managed as such, with resort to intravenous plasma or transfusion of whole blood, intravenous fluids and supportive medication (55). Paisseau & Lemaire (62) recommended the use of epinephrine in treating algid malaria, and the use of adrenal cortex preparations has been suggested (47). On theoretical grounds, the physiological properties of *l*-arterenol, which strongly supports peripheral vascular circulation and cardiac action with minimal cardiac irritation (63), suggest that this drug would be particularly useful for supportive therapy of algid malaria. Khan (64) supplemented specific treatment of cerebral malaria by concurrent intravenous injection of 50 to 200 mg. of nicotinic acid every 2 hr. until consciousness was regained. The object was to produce vasodilatation to counteract the occlusion of cerebral capillaries by falciparum parasitized red blood cells.

Specific therapy should be started as early as possible in all types of [illegible] may be fatal in acute fal- [illegible] he 8-amino- [illegible] ally require [illegible] eatment for secondary anemia may speed convalescence. The properties of the drugs currently available or interesting are reviewed below.

favors maintenance of an effective plasma concentration [Most *et al* (81)]. A single dose of 0 3 to 0.5 gm. of chloroquine base provides an effective plasma concentration for a week. Chloroquine rapidly alleviates clinical symptoms in all forms of malaria and radical cure of falciparum infections is usual [(79),(80), also Warthin *et al.* (82); Kamal & Abdel Messih (83); Halawani *et al* (84); Berberian & Dennis (85)] In comparative studies, clinical attacks were terminated in less time with chloroquine than with other drugs available [Canet (86); Coatney *et al.* (87); Butts (88); Menk & Mohr (89)] It is well tolerated by children and pregnant women (85), and is generally less likely to produce disagreeable side effects than is quinacrine, although transient blurring of vision, gastrointestinal distress, headaches, and urticaria may occur [Alving *et al.* (90)] Chloroquine is effective against plasmodia resistant to chloroguanide. Failure to respond to chloroquine has been reported from the Gold Coast for three of ten patients by Messent (91), but it is unlikely that "resistant" strains explain these failures Attempts to induce resistance of plasmodia of birds, monkeys, and man to chloroquine have uniformly failed (92 to 95).

Chloroquine hydrochloride may be injected intravenously or intramuscularly for treatment of acute malaria. Scott (96) cured falciparum malaria with a single intravenous dose; Culwell *et al.* (97), and Spicknall *et al.* (98) treated Chesson strain vivax malaria and induced falciparum malaria with one intramuscular dose of 200 or 300 mg chloroquine (base) or two doses of 200 mg. 4 hr. apart Absorption following intramuscular injection is rapid and peak plasma concentrations are obtained in about 15 min. Halawani & Baz (99) successfully treated malaria attacks with a single oral dose of 600 mg. chloroquine base Coggeshall (100) considers chloroquine the drug of choice for treatment of all types of malaria.

Chloroquine is a superior prophylactic suppressant under hyperendemic conditions [Berberian & Dennis (85); Himpe & Pierquin (101); Clark (102)]; the optimum prophylactic dose is 0 3 gm. chloroquine (base) as a single dose once weekly. Favorable tolerance and duration of action makes chloroquine ideal for mass prophylactic suppression and reduction of the splenic index even in the absence of mosquito control (103 to 106).

Hydroxychloroquine—Hydroxychloroquine (plaquenil, Win 1258) is 4-[1-methyl-4-(ethyl-2-hydroxyethylamino)butylamino]-7-chloroquinoline [Surrey & Hammer (107)] It is as active as chloroquine and about one-third as toxic [Dennis *et al.* (108)]. Loughlin *et al.* (109) obtained cure of 74 falciparum malaria patients using single oral doses of 1.0, 2 0 or 3 0 gm. of the diphosphate salt Hoekenga (110) treated 21 falciparum and 48 vivax malaria patients with a single oral dose of 1 25 gm , single intravenous infusions of 0 36 gm. were used for 14 other falciparum infections Prompt clinical response, rapid clearance of parasitemia, and superior tolerance suggest that hydroxychloroquine may be the most useful of the 4-aminoquinolines for treatment of malaria; its relative value for prophylactic suppression remains to be demonstrated.

Amodiaquin.—Amodiaquin (camoquin, cam-aqi, miaquin, SN 10,751) is

plasma concentrations than do other strains [Shannon *et al.* (67,68)]. Quinine is slow in producing relief of symptoms and in suppressing the parasitemia; it is further stigmatized by being a factor in precipitating blackwater fever. When administered concurrently with one of the 8-aminoquinolines (e.g., pamaquine), both suppressive and curative results are improved, but there is also an increased risk of toxic accidents (66).

Quinacrine.—(Mepacrine, atabrine, atebrin, acriquin, chemiochin, chinacrin, crinodora, erion, haffkinine, italchina, malaricida, metoquina). Quinacrine is 9-(4-diethyl-amino-methyl-butylamino)-6-methoxy-2-chloroacridine (69). Quinacrine is effective against the erythrocytic phase of all species of plasmodia and will usually terminate a clinical attack; in falciparum malaria a high rate of radical cures is obtained, but in vivax malaria relapses are not prevented. The suppressive activity of quinacrine is related to the concentration of free drug in the plasma [Smith *et al.* (70); Taggart *et al.* (71)]. Quinacrine is readily absorbed from the gastrointestinal tract, has a marked affinity for tissues, especially of the liver, and causes coloration of the skin and sclerae. In contrast to quinine, quinacrine is degraded and excreted slowly, hence its action is more prolonged. The maintenance of plasma concentrations greatly in excess of the effective range is limited by the tissue affinity and toxicity (66,70,71,72). The peripheral blood is cleared of parasites by quinacrine more quickly than by quinine, and clinical response is correspondingly more rapid. Concurrent medication with quinacrine inhibits the metabolic alteration of pamaquine [Zubrod *et al.* (73)], and quinacrine increases toxicity of concurrently administered pentaquine [Atchley *et al.* (74)]. The degree of susceptibility to quinacrine varies with different species and different strains of offending plasmodia (71,75,76).

Quinacrine inhibits both carbohydrate and protein metabolism of erythrocytic plasmodia [Fulton (6)] The action of quinacrine on erythrocytic stages of *P. vivax* is apparent microscopically within 4 hr. after oral administration of the drug (12,13); growth is stopped and degenerative changes appear in all growing stages. Quinacrine does not affect the infectivity of gametocytes of *P. falciparum* (13) or the development of oöcysts in the mosquito (77).

4-Aminoquinolines.—The most useful antimalarial drugs developed to date are certain 4-amino-7-chloro-quinolines. As a group, these drugs are well tolerated, rapidly effective, and exert prolonged suppressive action. They accomplish a high rate of radical cure of falciparum malaria, but do not affect the tissue stages of relapsing vivax or quartan malaria.

Chloroquine—Chloroquine (aralen, nivaquine B, resochin, tanakan, SN 7618, 3377 RP) is 4-(4-diethylamino-1-methylbutylamino)-7-chloroquinoline (78). It is completely absorbed from the gastrointestinal tract and concentrations attained in the plasma are substantially higher than with quinacrine [Loeb *et al.* (79)] Chloroquine has a high affinity for the tissues, particularly of the liver, spleen, kidneys, and lungs, as well as leukocytes; the rapid localization necessitates a "loading" dose to obtain a high plasma level quickly [Berliner *et al.* (80)]. A slow rate of degradation and excretion

Pentaquine and isopentaquine.—Pentaquine (SN 13,276), synthesized by Drake *et al* (128), is (8-5-isopropylamino-amylamino)-6-methoxy quinoline. Its action resembles that of pamaquine, but it is only one-third as toxic (129 to 132). However, it is still toxic enough to be subject to the same restrictions as pamaquine. The analog iso-pentaquine (SN 13,274) is somewhat more effective, on an equal dose basis, but also should be given only under hospital supervision (125,127,129).

Primaquine.—Primaquine (SN 13,272) is 8-(4-amino-1-methylbutyl-amino)-6-methoxyquinoline [Elderfield *et al.* (133)]. Primaquine, given in doses of 15 mg. base daily for 14 days with chloroquine or quinine, is more reliable for cure of relapsing vivax malaria than any therapeutic regimen yet reported [Edgcomb *et al.* (134)], and primaquine may be used in doses up to 30 mg. base daily [Alving *et al.* (56); Garrison *et al.* (135)]. Primaquine is well tolerated by Causcasians [Clayman *et al.* (136)]. It is somewhat more toxic to Negroes, but is well tolerated at an effective dose of 15 mg. daily [Hockwald *et al.* (137)]. *Primaquine offers the full curative and causal prophylactic* action of the 8-aminoquinolines and is the only member of the group to offer a sufficient margin of safety to be considered for mass prophylaxis (56).

Chloroguanide.—(Paludrine, proguanil, chlorguanide, diguanyl, drinupal, palusil, guanatol, titian, M 4888, SN 12,837) Chloroguanide is 1-(*p*-chlorophenyl)-5-isopropyl-biguanide (138). Adams *et al* (139) found it readily absorbed from the gastrointestinal tract and rapidly excreted through the kidneys. Chloroguanide has a wide margin of safety, produces radical cure of most strains of falciparum malaria and suppresses all other species [Maegraith *et al.* (140)]. It has some inhibitory effect upon the pre-erythrocytic forms of *P. vivax* [Fairley (141)], but is not a certain cure, relapses frequently occurring when the medication stops [Lints *et al.* (142)]. Clinical response to the drug is markedly slower than to quinine, quinacrine, or chloroquine [Jones *et al.* (143)], and it is, therefore, a less desirable drug for the initial treatment of acute malaria (144 to 148). Highly resistant strains of *P. falciparum* have been encountered in West Africa (147, 149, 150), in Eritrea (151), the Philippines (152), and New Guinea (153). By giving subcurative doses of chloroguanide it is possible readily to produce resistant strains in chicks (154,155), monkeys (156,157), and in man (95,158,159). Evidence is rapidly accumulating that in some regions previously susceptible plasmodia of man are acquiring resistance to chloroguanide (160 to 163). Gunther *et al* (153) reported that although chloroguanide was a satisfactory suppressant in New Guinea for three years, there was a progressive decrease in efficiency in the following 19 months with development of chloroguanide *resistant strains of all three prevalent species of malaria parasites*

The pharmacodynamic actions of chloroguanide, including inhibition of gastric secretion, have been reviewed by Vane (164). Thurston (165) and McFadzean (166) have described morphological changes in schizonts which indicate that chloroguanide acts by preventing completion of nuclear division. Gametocytes lose their power to develop in the mosquito [Shute &

4-(3-diethylaminomethyl-4-hydroxyanilino)-7-chloroquinoline dihydrochloride dihydrate [Burckhalter *et al.* (111)]. Its schizontocidal activity is about the same as that of chloroquine, but it acts slightly less rapidly [Coatney *et al.* (112); Singh (113)]. Under field conditions it has been generally satisfactory for treatment of acute malaria of all types, and is a useful prophylactic suppressant [Bertagna (114)] When amodiaquine is administered orally to man, the plasma concentration is notably less than that of chloroquine or sontoquine at corresponding doses (80). It has been used effectively for single dose (10 mg./kgm.) oral therapy of vivax and falciparum malaria [Halawani *et al.* (115); Hoekenga (116,117)].

Sontoquine.—Sontoquine (sontochin, nivaquine A, nivaquine C, SN 6911, 3038 RP) is 4-(4-diethylamino-1-methylbutylamino)-3-methyl-7-chloroquinoline (78). It was used by the German armies during the war for prophylactic suppression. It is an effective antimalarial, but requires more frequent medication than does chloroquine or amodiaquine which it resembles pharmacologically [Berliner *et al.* (80); Canet (86); Decourt & Schneider (118); Ruhe *et al.* (119); Gordon *et al.* (120)].

The 8-aminoquinolines.—Those derivatives of 8-aminoquinoline which have significant antimalarial activity are characterized by relatively high toxicity, selective activity against gametocytes, and a certain amount of activity against the persistent tissue phase of vivax malaria Suppressive action against erythrocytic schizonts is slow at safe dose levels. The 8-aminoquinolines have been regarded as curative rather than suppressive drugs, but their curative action is still a relative matter, subject to limitations imposed by toxicity as discussed below; activity is enhanced by concurrent use of quinine or chloroquine. Several new antimalarials of this class were developed by American chemists during World War II. This group of compounds may cause hemolytic anemia, especially in negroes.

Pamaquine.—Pamaquine, (pamaquin, plasmochin, plasmoquine, aminoquin, beprochin, gamefar, praequine, quipenyl) was the first synthetic antimalarial and is still the only 8-aminoquinoline which is widely available. It is 8-(4-diethylamino-1-methylbutylamino)-6-methoxy-quinoline (121). The

when used with quinacrine or chloroguanide, which cause high plasma concentration [Zubrod *et al.* (73); Atchley *et al.* (74); Decherd (124); Monk (125)]. Because of the narrow margin of safety between effective and toxic doses when used either alone or with quinine, pamaquine should be used only under strict medical supervision and preferably in a hospital (82,125). It should never be used for mass treatment or prophylaxis Pamaquine produces methemoglobinemia which is proportional to dosage; the effect is

[duration not stated], overt malaria did not occur during 251 days after the drug was stopped; it was concluded that the liver forms of *P. vivax* were probably destroyed.

Oakley (179) reported that pyrimethamine 10 mg. per kg. given daily to monkeys produced changes resembling those produced by antifolic-acid substances, and Goodwin stated that in experiments with dogs, large doses of pyrimethamine caused megaloblastic anemia, inhibition of leucopoiesis, and degenerative changes in the intestinal epithelium, similar to the effects produced by aminopterin and other antagonists of the folic acid system. Pyrimethamine is an extremely interesting antimalarial drug, but at this stage of evaluation the available evidence suggests that the slow therapeutic action and frequency of failures will discourage its use for treatment, and the hazard of natural or acquired resistance of strains will restrict its use for mass prophylaxis.

The ideal, all-purpose, inexpensive, antimalarial drug still awaits discovery, but in the meantime therapy and chemoprophylaxis may be effectively carried out. An appropriate combination of chloroquine and primaquine offers the greatest promise of providing those qualities stipulated in the introduction to this section of the review. It may be that primaquine supported by amodiaquine, chloroguanide, or pyrimethamine will also provide useful combinations, but the effect of these drugs on the toxicity of primaquine has not been reported.

AMEBIASIS

The human colon is the normal habitat of five species of parasitic amebas: *Endamoeba histolytica*, *Endamoeba coli*, *Endolimax nana*, *Iodamoeba williamsi* (*I. bütschlii*), and *Dientamoeba fragilis*. Of these, only *E. histolytica* is known to be pathogenic, the others are normally harmless commensals. Conventionally, the term "amebiasis" refers to infection of humans by *E. histolytica*. Craig (180) has used the term to emphasize the ubiquitous and protean nature of *E histolytica* infection, and to de-emphasize the "dysenteric" phase of the commonly misused appellation "amebic dysentery." Those physicians who believe that they are not encountering amebiasis in general practice are urged to consult Craig's masterful presentation of amebiasis and its clinical significance (180).

Geographic distribution and prevalence.—The incidence and distribution of parasitic amebas of man bear no relation to climate, but are directly related to toilet hygiene, and practices which favor dissemination and ingestion of feces.

The more acute clinical forms of amebiasis are most frequently encountered in the tropics, but *E. histolytica* infection is world wide in distribution, and fatal chronic infection may occur anywhere. The first description of amebas in intestinal lesions was by Lösch (181), in Russia. Epstein (182) reported the incidence of *E. histolytica* to be 60 per cent for natives of the Kala peninsula (inside the Arctic Circle), and 25 per cent for residents of Lenin-

Maryon (167)]. The limitation of the point of attack to one stage of the erythrocytic cycle is in contrast to the action of quinacrine and chloroquine which attack all stages of this cycle.

The antimalarial activity of chloroguanide has been attributed to the metabolite 1-*p*-chlorophenyl-2:4-diamino-6:6-dimethyl-1:6-dihydro-1:3:5-triazine, which was found to be 10 times more effective against *P. gallinaceum* than the parent compound [Carrington *et al.* (168)], but Schmidt *et al* (169) found this metabolite only one-half to one-fourth as active as chloroguanide when tested against *P. cynomolgi* in monkeys.

Pyrimethamine.—(B.W. 50–63, daraprim). Pyrimethamine is 5-(*p*-chlorphenyl)-2:4-diamino-6-ethylpyrimidine, described by Falco *et al.* (170,171) Hitchings *et al.* (172,173) found many 2:4-diaminopyrimidines to be potent antagonists of pteroylglutamic acid *in vitro*. Pyrimethamine was found to be 50 to 200 times more effective as a suppressive than chloroguanide when tested in the laboratory against *P. gallinaceum* in chicks. *Plasmodium berghei* in mice, *Plasmodium cathemerium* in canaries, and *P. cynomolgi* in monkeys; the drug was ineffective as a causal prophylactic but was effective against chloroguanide resistant strains [Rollo (174)]. Acute toxicity was found to be very low. Archibald (175) found pyrimethamine to be well tolerated by humans, and doses as small as 5 mg. cleared most of the trophozoites of *P. falciparum* and *P. malariae* from the blood within four days. A single 25 mg. dose appeared to exert suppressive activity for a month, and side effects were not observed in 22 children given that dose. Goodwin (176) and Schneider *et al* (177) confirmed the suppressive activity of pyrimethamine against *P. vivax* and *P. falciparum*. Foy & Kondi (178) found that pyrimethamine in the plasma rendered *P. falciparum* gametocytes noninfective for mosquitoes.

A recent symposium on pyrimethamine (179) brought out the following additional observations. Resistance is readily produced in the laboratory by undertreatment, indicating that adequate dosage must be assured in using the drug as a prophylactic suppressive Clinical trials in Gambia, Tunisia, Indo-China, and Assam had shown that single doses varying from 20 to 100 mg. had been effective in treating active infections of *P. falciparum*, *P. malariae*, and *P. vivax*, though occasional failures had been encountered. Field, Edeson & Wilson (in Malaya) were dissatisfied with pyrimethamine because it acted slowly, some patients having severe symptoms for three days after the dose It had failed to eradicate asexual *P. falciparum* parasites in 13 of 80 cases, and increasing the dose did not greatly improve the proportion of successes However, there were no failures among 22 cases of vivax malaria. Wilson stated that in view of his experience, pyrimethamine is unlikely to replace chloroquine in Malaya. McRobert reported that parasites of the Korean strain of *P vivax* had been found in the blood of patients six and a half days after commencing treatment with pyrimethamine. Boyd referred to experiments by Coatney on prisoner volunteers at Atlanta, Georgia, wherein subjects were infected by bites of *P. vivax* infected mosquitoes and then given varying doses of pyrimethamine In those receiving 25 mg. weekly

sociated with superficial erosions and patchy low-grade chronic inflammatory reaction involving dilated cystic solitary glands of Lieberkuhn. The trophozoites are found in the gland crypts, and probably enter the tissues near the mouth of the glands, where they pass directly into the interglandular papilla of the lamina propria (197). Invasion may never progress beyond this superficial state in the so-called "asymptomatic" carrier. The presence of the ameba leads to death and necrosis of contiguous tissue cells without necessarily provoking much cellular reaction. If the number of trophozoites is low, reparative proliferation may hold the infection in check, but if the infection is heavy because of a large infective dose or rapid multiplication of the parasites, there is a lateral spread of the lesion from the base of the gland resulting in production of characteristic, pin-point, flask-shaped ulcers. Such adjacent ulcers may coalesce, causing sloughing of intervening mucosa to form the typical "Dyak hair" ulcer characterized by hair-like projections of the supporting tissues as the residual base, and a ragged undermined edge. Microscopically, sections of even small ulcers often show trophozoites of *E histolytica* within the lumen of involved blood vessels, and it must be assumed that many of the parasites are transported to the liver where they are either destroyed or eventually produce hepatitis or abscesses.

There are two recognizable races of *E. histolytica*, characterized by size. The large race is relatively more pathogenic and is characteristic of severe acute infection. The small race is more characteristic of the milder chronic infections or asymptomatic carriers, and is considered by some specialists to be a separate species (*Endamoeba dispar, E. hartmanii*).

There are at least four clinical phases of intestinal amebiasis [Armstrong (199)], namely: (*a*) "Asymptomatic" carriers, without history of diarrhea, recognized by identification of cysts in the feces, (*b*) Nondiarrheic "cyst passers" with ill-defined gastrointestinal or extra-intestinal or both symptoms resulting from amebic infection; (*c*) Acute amebic dysentery and acute dysenteric exacerbations of chronic amebic colitis; (*d*) Post-dysenteric infective colitis, in which amebic ulceration is complicated or followed by shigellosis, ulcerative colitis, etc. [see Stewart (200)].

Extra-intestinal amebiasis may be concurrent with or subsequent to any of the above phases of intestinal amebiasis. The first two categories may properly be considered as representing degrees of severity of subacute amebiasis

Extra-intestinal amebiasis occurs most frequently as amebic hepatitis or liver abscess. Metastatic abscess of the brain, spleen, or other organs occur. Perforation of liver abscess may lead to pulmonary amebiasis, pericarditis, peritonitis, or perforation of the body wall. Obviously extra-intestinal amebiasis is a serious matter and makes amebiasis a surgical as well as a medical problem. The surgical aspects of hepatic amebiasis have been magnificently reviewed by Ochsner & DeBakey (201). The desirability of assuming the existence of some degree of hepatic involvement in all cases of intestinal amebiasis is supported by the fact that development of hepatic abscess is not necessarily related to the clinical severity of the primary intestinal infection.

grad, as compared to 4.8 per cent in the Ural region and 10.4 per cent in Baku. Other representative temperate zone survey findings are: 5.7 per cent in Northwest Germany before the war, and 16 to 50 per cent after the war [Bach (183,184)]; 10 to 15 per cent in North China [Tao (185); Faust (186)]; 7 to 10 per cent in Britain [Dobell (187)]; and 31 per cent in the province of Santiago, Chile [Neghme & Silva (188)]. The over-all incidence of amebiasis in the Western Hemisphere is estimated to be 20 per cent [Faust (189)].

In the United States the incidence of *E. histolytica* infection in the general population is 10 to 20 per cent [Craig & Faust (190)], and more recent figures do not modify that estimate. Among institutionalized mental defectives the incidence may be as high as 71 per cent [Tobie *et al.* (191); Berberian *et al.* (192)].

Available morbidity statistics on amebiasis are unreliable, and reported deaths undoubtedly offer a better index of the occurrence of the disease. Wright (193) has provided data showing that an average of 236 deaths from amebiasis were reported annually in the United States during the 14-year period 1933 to 1946 inclusive; about 36 per cent of these 3305 deaths were reported from northern and western states. During the same period, approximately 3000 cases were reported annually, but in some areas the number of reported deaths from amebiasis exceeded the case reports. Amebiasis and acute amebic dysentery are most prevalent in Texas, Louisiana, and Mississippi.

Pathogenicity of E. histolytica.—The potential pathogenicity of *E. histolytica* has been clearly established since the classical studies by Councilman & Lefleur (194) and Walker & Sellards (195). Dysentery is the primary manifestation of the acute disease, and is often complicated by extension of the amebic infection to the liver. However, even in the tropics, the disease is more frequently seen as a chronic subacute condition, often with only vague nonpathognomonic abdominal symptoms. In cooler climates the onset of the disease is usually so insidious, and the symptoms are so varied, that it is likely to be overlooked.

Endamoeba histolytica has only two significantly different forms in its life cycle: the motile ameboid trophozoite and the passive encapsulated cyst. Infection is acquired by swallowing mature tetra-nucleate cysts. Excystation presumably occurs in the ileum, resulting in four small trophozoites which increase in size and then multiply by simple binary fission.

The optimum habitat is the large bowel, and the favored sites of multiplication are pendant portions where stasis and trauma to the mucosa are most likely to occur. Early multiplication undoubtedly occurs in the crypts and mucous coat; there are numerous reasons for doubting that multiplication ever occurs in the fecal mass. Cysts never participate in the production of lesions.

[illegible] natural infection in monkeys [illegible] studies on accident victims [illegible] *istolytica* is almost always as-

other co-existing elements, and in the presence of a positive laboratory report of *E histolytica* cysts in the stool, therapeutic trial with a safe effective intestinal amebacide provides a valuable aid for differential diagnosis. Even in the case of the truly asymptomatic cyst passer, the possibility of subsequent pathogenesis in the intestine or liver places a burden of responsibility upon the informed physician who chooses not to treat. Musgrave (209) reported a study of 50 fatal cases of intestinal amebiasis without diarrhea.

Treatment of amebiasis—There have been numerous extensive reviews of the chemotherapy of amebiasis [Armstrong (199); Shookhoff (205); Hargreaves (210); Anderson & Hansen (211); Dennis *et al* (212); Bargen (213)]. The treatment of amebiasis is not a straight-forward matter. There is no known amebacide which will clear all cases of intestinal amebiasis without a parasitological relapse rate of at least 10 per cent if the cases are adequately followed up Those amebacides which are most useful for treatment of intestinal amebiasis are ineffective against hepatic amebiasis and those drugs which are effective against hepatic amebiasis are unreliable against the intestinal parasitism (210, 214).

The effective antiamebic drugs include the plant alkaloids, emetine and conessin, the arsenical compounds bismuth glycolylarsanilate (Milibis), carbarsone, and thioarsenite (Thiocarbarsone); the halogenated hydroxyquinolines chiniofon, diiodohydroxyquinoline (Diodoquin), and iodochlorhydroxyquinoline (Vioform); the antibiotics Aureomycin, Terramycin, Bacitracin, and possibly Fumagillin, and for extra-intestinal amebiasis the well known antimalarials chloroquine and quinacrine.

Emetine hydrochloride is most useful because of its prompt pharmacodynamic action in stopping diarrhea; it is a poor amebacide [Hargreaves (210); Sodeman & D'Antoni (215); Sodeman (203)] Conessin (Kurchi) is less toxic for the heart, but causes psychic disturbances requiring concurrent administration of sedatives [Canet (216)] Diiodohydroxyquinoline has been the most popular of the iodo-hydroxyquinolines as an intestinal amebacide, but recently certain arsenicals and the antibiotics have gained favor (203). Bismuth glycolylarsanilate has been proven to be a superior intestinal amebacide with remarkably little toxicity (217 to 225). Bismuth glycolylarsanilate is ineffective in acute dysentery until the diarrhea has been arrested sufficiently to retain the highly insoluble drug. Thiocarbarsone has been found effective in subacute amebiasis [Anderson *et al* (226), Sodeman (203)]; wider use will permit evaluation of its tolerance. All of the arsenicals are likely to cause toxicity in sensitive patients The antibiotics aureomycin and terramycin compare with emetine in controlling the symptoms of acute amebic dysentery, but relapses are frequent (227 to 232) For initial treatment of dysentery the antibiotics offer the advantage of being effective against shigellosis and mixed infection Bacitracin is less effective than terramycin, and fumagillin has not been adequately evaluated (203).

Hepatic amebiasis may be treated with emetine (210), but chloroquine proved to be highly effective [Conan (233, 234, 235); Manson-Bahr (236);

In fact amebic liver abscess without concurrent intestinal infection and without history of diarrhea is not uncommon [Banker (202)].

Symptomatology.—In the United States over 95 per cent of the patients with amebiasis do not have active diarrhea [Sodeman (203)]. Because other symptoms presented are those frequently seen in more common conditions, the attention of the physician is diverted from amebiasis as a possible diagnosis. The group of patients with no symptoms is said to be a large one, but probably is less than 15 per cent. Actually, most people with minor symptoms have become so accustomed to them that they are accepted as normal; even periodic appearance of blood and mucus in the stool may be accepted by the patient as normal, and symptoms may be denied. Such "asymptomatic" patients are detected only in surveys or routine stool examinations, but they frequently note improved health after specific treatment [Towse *et al.* (204); Shookhoff (205)].

Amebiasis frequently causes only low-grade general symptoms such as tiredness, anorexia, asthenia, headache, and other components associated with neurasthenia. Patients are often treated for long periods for neuroses, and such management may result in a degree of fixation that requires psychotherapy after clearance of the amebic infection. It is also true that psychoneurotic patients may have amebiasis without any causal relationship. Abdominal tenderness, particularly over the cecum and gall bladder, is present in more than 50 per cent of subjects with cyst positive stools, and should always suggest that stool examination be carried out. Sodeman (203) has emphasized the importance of epigastric distress and dyspepsia, suggestive of gastric or duodenal disease, in diverting attention from a diagnosis of amebiasis Because of the very wide variety of symptoms presented by subacute amebiasis, and the importance of the disease as a cause of marginal ill health, there is probably greater need for routine stool examinations than there is for routine serological tests for syphilis

Definite colonic symptoms of amebiasis include distention, tenderness of [illegible] ...a, [illegible] nt [illegible] u-topsy studies by Clark (206) have shown that the percentage frequency distributions of lesions is: cecum 87, ascending colon 57, hepatic flexure 4.7, tranverse colon 6 3, splenic flexure 12.6, descending colon 4.7, sigmoid 33, rectum 39. This distribution of lesions is reflected in the signs and symptoms, and suggests the proportion of cases which would be missed if undue reliance were placed on the results of sigmoidoscopic examination.

In relation to the relevancy of symptoms, or lack of symptoms, the justification for treating cyst passers has often been questioned (207, 208). In view of the nature of the symptoms in many cases of amebiasis, the validity of the diagnosis can be tested only by therapeutic trial (199). It should be assumed that any competent physician would take the steps necessary to assure himself that the symptoms presented are not from malignancy or

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Basneuvo *et al.* (237); Harinasuta (238)]. It has been effective in emetine resistant liver abscess [Murgatroyd & Kent (239); Emmett (240)] Conan has found sontoquine to be effective also (241), and quinacrine may be useful [Radke (242)].

The management of amebiasis in institutions caring for low-grade mental defectives is a particularly serious problem, and deaths from extra-intestinal complications are not infrequent. Because bismuth glycolylarsanilate and chloroquine are both well tolerated, they have been used in combination for suppression and prophylaxis. Berberian *et al.* (192), in a carefully controlled study, were able to suppress the incidence to 9.5 per cent (daily medication) and 25 per cent (weekly medication) in the presence of 71 to 76 per cent incidence in the control groups. This combined medication is effective under field conditions for simultaneous control of amebiasis and malaria [Hoekenga (243)]

Laboratory diagnosis.—Modern criteria for the laboratory diagnosis of amebiasis have been discussed recently by Faust (244). For technical procedures the reader should consult Craig & Faust (190). Diagnosis requires positive identification of trophozoites or cysts of *E. histolytica*. Stool specimens to be examined in a distant laboratory should be preserved with polyvinyl alcohol (245, 246). In our opinion the identification of cysts in casual stools is more reliable than using purged specimens, but the latter should be used if cysts are not found and there are clinical grounds for suspecting amebiasis. In examining formed stools, the mucus coated surface should be sampled for cysts and precystic forms from the lower bowel; cysts deeper in the fecal mass suggest lesions in the cecum and upper colon. The zinc sulfate concentration procedure and the iodine stain can replace iron-hematoxylin stained slides for routine diagnosis. Coelho (247) has found sampling by rectal swabs to be useful.

The complement fixation test is of value for supporting a diagnosis of extra-intestinal lesions, but is completely unreliable for the unsupported diagnosis of intestinal amebiasis [Hussey & Brown (248)]. Proctoscopic examination, and examination of material obtained by aspiration are very valuable, but only 20 to 42 per cent of positive cases can be detected in this manner [Browne *et al.* (249)]. The difficulties of laboratory diagnosis af amebiasis have been unduly exaggerated.

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PLASTIC SURGERY: WOUND CARE AND SKIN GRAFTING[1]

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A survey of the recent literature of plastic surgery reveals that much thought and ingenuity have been devoted to the application of the special techniques and procedures of plastic surgery to widely diversified surfaces, systems and organs of the body.

The breadth of these studies is indicated by publications on congenital facial defects (1 to 5), the effect of trauma to the growth centers of the mandible (6), the repair of congenital and traumatic defects of the male genitalia (7) and of the hands and feet and even a method for maintaining the patency of the Fallopian tube in the correction of sterility (8).

While the average practitioner may find such subjects of only occasional interest, nearly everyone has use of the accumulated knowledge related to the problems of skin transplantation Recent advancements in medicine have caused many changes in the problems of skin grafting. Medical achievements have made it possible to bring patients through hitherto fatal injuries and illnesses to the point where skin coverage and massive wound closure become the factors most important for their survival or rehabilitation

The invention and perfection of mechanical apparati for cutting skin grafts has made it possible for the inexpert to procure good skin grafts. This ability has in turn directed the interest of a great number of practitioners to formerly neglected conditions. Even though an understanding of the physiology and mechanics of wound healing has long been available, wishful thinking has often caused a hopeless reliance to be placed on ineffective drugs As a result, wounds or degenerative surface lesions requiring skin grafting became chronic and disabling. This tendency is resisted by a better knowledge of the techniques of skin grafting, even though the widespread dissemination of inaccurate claims such as the beneficial stimulation of spontaneous epithelization by ACTH was harmful (9).

Modern surgery has devised operations which depend on skin transplantation for their successful completion. An example is the restoration of the pharyngeal continuity immediately following radical extirpation of malignant tumors (10). Better operations for cancer of the breast are possible when the surgeon feels free to excise more skin because of his ability to produce primary healing with an immediate skin graft. Draper *et al* (11) have shown that replacement of bladder epithelium by skin grafts can be done experimentally.

It is the purpose of this chapter to review some of the basic conditions

[1] The survey of literature pertaining to this review was completed in November 1952.

requiring the transplantation of skin, and to describe how we think these situations should be handled.

Burns

The treatment of the severely burned patient provides a good example of the need for skin grafts, and also illustrates many of the changes that recent advancements have made in the problem of skin grafting as a whole. Burns are common in many fields of practice, but their importance is further emphasized by McDowell (12) using the following information released from the Department of Defense, the National Security Resources Board, and the Office of the Surgeon General. As noted, a surprise air burst of an atomic bomb at about 2,000 feet over an urban area at noon in the summer would be expected to produce 120,000 casualties with about 40,000 immediate deaths. Between 60 per cent and 85 per cent of the 80,000 survivors would have thermal burns, 30 per cent of them being classified as severe. Aside from concomitant injuries these burns, and indeed all burns, present an acute problem.

A burn results from exposure to excessive radiation or heat The surface injury may be classified as either superficial or deep, depending on whether there are remaining viable epithelial elements or whether the injury has completely destroyed the full thickness of skin. The burn injury also produces acute physiological and constitutional complications which can be insurmountable. Advancements in the field of burn physiology have changed the picture of burn therapy considerably.

The handling of the acute wound has been the subject of debate for centuries. Recently, for example, Wallace (13) has popularized the exposure treatment of burns, but he adds that "No one method of local care has all the answers." Allen & Koch (14) stress the essentials of burn care as consisting of (*a*) preventing and combating shock; (*b*) converting the open contaminated wound into a clean wound; (*c*) covering the wound with a simple dressing; (*d*) keeping the injured part at rest; and (*e*) securing healing in the minimum period of time and with minimum loss of function Colebrook (15) places his emphasis on the role of infection as related to burns.

In addition to the local care of the burn, the general care of the patient is of even greater importance in the early stages. The problems of shock, hemoconcentration, electrolyte imbalance, and anuria as pointed out by Evans (16) change from hour to hour. Considerable attention has been directed along these lines, and as a result many severely burned patients have been carried through this period of initial physiological upset to a point where they are much more stable and the matter of wound coverage then becomes all important.

The salvage of function in a deeply burned hand, face, or other critical part is often a problem of early skin grafting, even though the patient as a whole may have relatively little damaged tissue. The preservation of function of a grosser part, the restoration of the patient to his proper position eco-

nomically, and in some instances the saving of life, even in the burn of moderate extent, is a similar problem. The conclusions of Moyer (17) have placed the problem of improving the survival rate of the severely burned patients with rather brutal force squarely upon the ability of the surgeon to resurface the denuded area quickly. These conclusions, reached after exhaustive statistical study, are:

Of 100 burns of all types and severity, the survival rate might be 5 per cent higher today than in the time of Dupuytren. Even today a patient with 56 per cent or more burn of body surface if carried through the stage of shock will probably die at the same rate as 100 years ago

Formerly, most patients dying from burns died during the first 48 hr. Now, with a better understanding of the therapy of the acute burn, such patient live longer, the severe deep burn may die of his debilitating ulcer perhaps weeks later, whereas the elimination of this ulcer would be curative It may be readily seen that an increased early salvage rate means inevitably an increased late death rate and a total of more patients sustaining burns on whom skin grafts must be considered.

Thus, the patient who has suffered a deep burn rapidly progresses to the stage where the problem is that of an open ulcer regardless of cause. This is characterized by fever, infection, loss of critical elements from the open surface, interference with nutrition, pain and a mental depression attending a painful and prolonged illness, all in proportion to the area involved. Large surface wounds resulting from conditions such as meningococcemia, symbiotic infection, mangle injury, or pressure necrosis may present the same local picture of still attached necrotic tissue, adjacent cellulitis, and the open wound Formerly such wounds were properly cared for by frequent dressings at which time necrotic tissue was washed or picked away as the patient would permit Dressings were often kept wet with Dakin's solution or saline, and the patient was tubbed in saline baths The goal was the attainment of a clean wound of compact red granulations free of slough and attended with a minimum amount of discharge, this being achieved with the least amount of pain and in the shortest time possible prior to grafting Properly performed, this procedure resulted in a wound suitable for the skin graft in from three to six weeks from the time of injury. However, the wet dressings were soggy, cold, and uncomfortable and the baths were time-consuming A great amount of nursing and medical care was needed, to a degree which is impractical in most hospitals today

In an effort to speed the process along, chemical debridement in the form of pyruvic acid paste was tried (18, 19). This was found to be painful and questionably effective. Search still continues for a biological solvent or enzyme which will digest away dead tissue in a rapid, painless manner without harming even the injured living cell. Although some progress is reported, the methods appear expensive and lacking in efficacy (20, 21). At present they are not adequate

The advent of simple, more pleasant anesthetic agents which may be administered frequently without toxic effects or prolonged interference with the patient's food intake has elevated the preoperative preparation in part from the bath and dressing room to the operating room. Here, by thorough cleansing associated with knife debridement, dressings are carried out quickly, effectively, and painlessly. In many instances a noninfected eschar is completely excised and the resulting surface grafted at once or a day or so later. This may be accomplished in 6 to 10 days after the receipt of the injury. In other instances, where the degree of infection does not permit this maneuver, the wound may be made receptive in shorter period of time than before by washing and debriding every other day under anesthesia. Pickrell (22) had reported the efficacy of self-administered trichlorethylene for analgesia and anesthesia during this process.

During the interval of preparation, the wound must be protected from additional trauma which may accrue from chemical, bacterial, or mechanical sources No "fertilizer" has been found to promote the growth of skin, and drugs used must be of a bland and protective nature. Mild ointments in sparse amounts impregnating fine meshed gauze which does not adhere minimizes trauma of chemical and mechanical nature. Dressings must not impound purulent material, and washing of the wound should not injure new tissue (23).

Every effort is thus made to convert a deep injury into a clean wound and the open wound into a grafted healed surface with such rapidity that the patient is not subjected to the rigors of a prolonged wasting illness and his delicately functioning parts are not distorted or fixed by scar and immobilization.

Maintenance of nutrition is important in direct proportion to the size and duration of the large open wound With a less critical total area of ulceration, the patient's nutritional balance may be maintained by more or less heroic efforts to introduce needed elements. Blocker's scheme (24) of a 24-hr. routine of motor injected high protein material at a carefully regulated rate through a small plastic nasal tube insures the maximum intake. Such a patient cannot be maintained in nutritional balance, however, if the open wound is of sufficient size Harkin's analogy (25) of the "leaking bucket" is very explanatory. Such a patient cannot be "filled" if the rate of "leak" *is too great The only hope lies in plugging the leaks.*

Moore (26) has described the state of chronic shock into which the ulcerated patient sinks Too often a patient's condition is described as good because the blood chemistry has been brought near normal by transfusions. Such an artifical and temporary build-up does not reflect the total body chemistry. Often the patient with the large deep wound can be brought to the stage where the wound is receptive to grafts but his unburned area is [illegible] skin for covering. Such a [illegible] can be plugged, because [illegible] loss created by infection

and by weeping through the open surface. It is in such a patient that the acute emergency must be met by the application of homografts taken from other donors in such an amount as to insure near complete, if temporary, healing. Homografts taken from an identical twin should survive permanently (27) All other homografts will take with normalcy but can be expected to be progressively lost after an indefinite persistence of from three weeks to seven mouths (28). ACTH and cortisone have failed to do more than increase the dangers of infection and have shown no clinical evidence of prolonging this persistence. These homografts, perhaps applied simultaneously with thin split-thickness grafts from the patient's own body provide a period of healing and recovery that can tide a patient over a critical period and may mean eventual recovery. As the homografts degenerate they may be replaced by additional skin grafts from the patient's own body, or by spontaneous healing The above concept further indicates the futility of "pinch" grafts which do not plug the "leaks" with sufficient rapidity to reverse the patient's course.

Antibiotics have helped in the control of invading infection but have been of little assistance in sterilizing an open wound, whether used locally or parenterally. It is immediately obvious that the greatest contribution possible in the treatment of the large area burn would be the development of a measure to make the survival of homografts permanent, or at least to prolong their usual length of survival

Blocker (29), along with others, has studied this problem and states that the most generally accepted theory of the etiology of homograft dissolution is that proposed by Medawar [previously described and published by Brown & McDowell (23)] which postulates that an immune response is acquired during the early survival period of the grafted tissue as a reflection of the genetic diversity existing between two individuals of the same species Blocker postulates that on the basis of genetic diversity within a single species, it would be expected that the greatest antigenic variation in the proteins of cells from the same basic tissue would be found in the nuclei This theory is borne out by the well-established fact that the only proven permanent homograft survivals have been in identical twins where there is the same nuclear composition He felt that Streptodornase, which acts specifically on nucleoprotein, might initiate enzymatic debridement of those damaged cells of the homologous graft which probably provide the antigenic stimulus to the recipient host during the first few days following the transplantation of the tissue. He found that the application of a single large dose of Streptokinase-Streptodornase at the time of transplantation prolonged the survival of the individual homografts. His results are not conclusive but show a trend in the study of this problem It has been observed repeatedly that a second set of homografts from the same donor is destroyed in an accelerated manner, a result presumably of the established immune reaction.

Observation of patients referred for skin grafting has led us to believe that confusion exists regarding the details of wound care and what is required of

the recipient area for the successful "take" of a graft. Regardless of the initial care of the burn, a time comes when the wound tends to become odorous, to be covered with crusts or shreds of necrotic skin, to exude foul discharge, and to be increasingly painful. This undesirable situation must be strenuously combatted by an organized program and well outlined objectives. During this intermediate period of sustained discomfort and disability in the severely and deeply burned patient a basic philosophical approach must be taken. In spite of changes in methods and techniques, the necessity for gentleness and kindness will remain. Good general nursing care, cheerfulness, and optimism will go a long way in caring for these individuals. It goes without saying that a close watch must be maintained to prevent unsuspected drops in protein and hemoglobin levels, and that the local condition of the wound reflects in part the general condition of the patient.

The goal is the successful application of skin grafts at the earliest time, in the fewest operations, with the greatest preservation of function possible The take of a split-thickness skin graft presumes a recipient site with minimum surface infection and an adequate blood supply on which the graft is held with stable, even contact. Realization of this aim requires lots of work, the application of technical knowledge, and attention to details in the wound preparation The execution of this procedure requires considerable surgical judgment

A team of adequate size to carry out dressing procedures rapidly relieves the overburdened operating room and minimizes the patient's anesthesia time The dressing should be scheduled so as to cause the least interference with the patient's food intake Dressings of large wounds are done in the operating room under analgesia or anesthesia if required. The wounds are washed thoroughly but gently with copious amounts of soap and water. Further cleansing with fat solvents, such as ether, may be necessary to remove accretions. Knife excision of necrotic material is done at the level of viable tissue. The patient is dressed with fine mesh gauze next to the wound. Good quality (44 gauge) roller bandage of the closely woven sort is adequate [2] This layer of fine mesh gauze may be lightly impregnated with an ointment. The roller bandage can be so impregnated with vaseline by sterilizing the intact roll in contact with the ointment. Over the layer of ointment-impregnated gauze, a bulky amount of absorbent dressing material is applied, and

[2] Although the point has been stressed in this medical center since 1928, and many times elsewhere, its importance is often overlooked Fine mesh gauze allows the discharge of fluid material but does not adhere or permit protrusion of granulation tissue through the meshes so as to rivet the gauze to the wound as does coarser material. We have seen patients admitted weeks after injury with bits of Turkish toweling incorporated within granulations Although less esthetic to consider, this material is no more injurious than the coarse dressing gauze often used next to granulating wounds. Constant vigilance is necessary to keep the supply personnel of most hospitals from reverting to the use of coarse meshed gauze in the preparation of vaseline or other greased gauze.

this is firmly bandaged in place. The bulk of the dressing must be adequate to insure firm, even pressure and splinting of the region. This serves to control edema of the entire part and to insure compact healthy granulations "Exuberant" granulation tissue is edematous tissue which may be made into a compact, red, and more healthy surface with less discharge, less infection, and a better minute blood supply through the action of pressure. The use of silver nitrate or other escharotics is harmful and results in necrotic tissue, increased infection, and a retarded wound.

Such wounds are dressed frequently, at least at 48 hr. intervals. The mechanical removal of purulent exudate and material reduces the infection just as surgical drainage of an abscess reduces infection elsewhere in the body.

Additional drainage may be promoted by using a wet to dry dressing. In this case, the fine mesh gauze is not ointment impregnated but is wet along with the overlying bulky dressing material. Normal saline or some other nontoxic, nonirritating fluid is used. Pressure is maintained. This dressing is bulky enough to retain moisture for a 24 to 48 hr period and should be changed daily. Wet dressings may be alternated with those of grease gauze or used continuously as judgment dictates.

An open would is ready for grafting when free of avital tissue, cellulitis, and undue contamination. This is evaluated from its appearance as well as the amount and character of the discharge Small granulating wounds may may often be rendered nearly sterile while larger ones are never so clean bacteriologically. Cultures of the wound are not used as criteria of readiness for grafting. The presence of *Bacillus pyocyaneus* infection as recognized by its green appearance and characteristic odor is a contraindication for operation. *B. pyocyaneus* is best eliminated by frequent soap and water cleansing and the omission of wet dressings for a time.

Smaller wounds of a less painful nature may not require such a sizeable and complicated set-up, but preparation for grafting should be no less thorough. Patients with ulcerations of the lower extremity should have final preparation during a period of bed rest Ulcerations permitting wide excision should be free from cellulitis, but do not require long preparation if the area can be excised without contamination of the field.

A tunnel, such as may be present in the axilla following loss of a radical mastectomy flap or along a tendon sheath, is usually a contraindication for a graft, as it will harbor bacteria which may cause loss of the adjacent graft. To obtain cleanliness, such sinuses should first be healed or opened by incision

Chronic Ulcerations

Chronic ulcerations of the lower extremity or elsewhere constitute a trying problem in every clinic. These patients in many instances are unable to work, are denied employment, and often become economic parasities. These ulcerations may be caused at the onset by any one of many conditions rang-

ing from local trauma or infection to a general circulatory disorder of the extremity. All too often the ulceration persists after the original causative factor has been controlled or after the circulatory disability has been improved in so far as may be possible. The patient is then dismissed to carry on in an unsatisfactory and haphazard manner.

In order to appreciate the therapeutic possibilities, the underlying pathology of the ulcer must be understood. An open wound heals by the formation of granulation tissue in its base which in turn is converted into scar which then contracts, reducing the total wound size. At the same time there is an ingrowth of epthelium from the borders. It must be remembered that this capacity for epithelial ingrowth is limited, and that the product is not normal skin but rather scar epithelium lacking in thickness, elasticity, and a firm attachment to the underlying scar. The greater the distance such epithelium travels, the poorer its quality, the greater its fragility, and the slower its progress. As more granulation tissue and scar is formed in the base, the vascularity of the ulcer is reduced. Such a wound cannot be healed permanently regardless of care, without correcting the underlying local factors It is no longer a varicose ulcer or a traumatic ulcer but is an "ulcer *per se*" (28). Proper treatment consists of the elimination of general factors, including circulatory and nutritional deficiencies as much as possible. This should be followed by a period of rest, elevation, wet dressings, and local care to minimze infection. When these are accomplished the ulcer is excised widely and deeply to eliminate avascular scar of inadequate quality. This excision must be carried to the point where the remaining tissue is soft and has a minute blood supply instead of an occasional bleeding point surrounded by areas of fibrosis which do not bleed. An immediate split skin graft of intermediate thickness is applied. Such grafts usually do well immediately, but must be properly cared for during their "seasoning" stage The extremity is kept elevated two to five weeks post-graft with frequently changed pressure dressings in place. The shorter period is adequate for smaller and more simple problems The patient may walk with crutches at the end of this period provided a pressure dressing is in place at all times when the foot is dependent. Without this supportive dressing the graft becomes congested and may be destroyed by spontaneous bleeding at its point of adherence to the base. Cautious weight-bearing is initiated in from three to six weeks, depending on the original problem. An elastic stocking or bandage must be worn permanently if the circulation of the extremity demands support. If the problem was of a purely local nature, elastic support must be maintained until the graft does not become congested in appearance when in a dependent position.

Pedicle Flaps

An occasional deep loss over the tibia may require the application of a pedicle flap. This is especially true of patients with ununited fractures of the tibia, chronic osteomyelitis, and particularly where a bone graft is contemplated. A local flap rotated to the ulcer site brings in additional blood

supply, and its donor site is covered with a split thickness graft. (30, 31). A cross-leg flap provides heavy covering but less increase in the local blood supply.

The sole of the foot constitutes a special problem of integument because of the demands as to comfort and permanency associated with weight-bearing. Traumatic losses from burns and crushing injury are frequent, but the need for removal of a plantar wart resistant to the usual conservative treatment is probably more common. Many such resistant warts have received excessive radiation with resulting skin damage and absorption of the underlying padding. Not only is the pain crippling, but the radiation dermatitis is dangerous and must be considered as premalignant.

Pedicle flaps on the sole of the foot from elsewhere on the body are undesirable but must be employed occasionally, especially for deep and extensive tissue loss over the heel or lower heel cord region. Other measures should be considered before the application of such a flap is decided upon. A free graft of thick split or full thickness skin is adequate in this region if sufficient underlying padding is present. If not, local flaps of sole of the foot tissue may often be rotated from under the instep, the base of the toes, of the side of the foot to the pressure area, the donor site being covered with free skin graft. Again the graft must be protected adequately throughout its "seasoning" period.

Patients with pressure sores have constituted a distressing and often hopeless group from the economic, humanitarian, and nursing standpoint. Better management has been forced only through the greater size of the problem as the number of paraplegics has mounted. The establishment of paraplegic centers has permitted the grouping of many of these patients, and has provided an opportunity for the individual surgeon to benefit from a concentrated experience while being assisted by those equally expert in caring for the patient's nutritional, nursing, and coincidental problems The trend has been toward more radical excision of the ulcer and underlying bone (32). This is accomplished by excision of the ulcer and the provision of a moveable healthy pad of skin and subcutaneous tissue over the ulcer site with the elimination of all possible underlying bony prominences. The donor site of the covering tissue is usually a local nonpressure area and is resurfaced by split grafts. As such patients have received better treatment and fewer have been bedfast there has been an increase in the percentage of ischial ulcers produced by sitting. This has led to the operation of complete ostectomy of the ischial tuberosity with trimming of the ischial rami to provide a broad flat surface on which to sit

Sacral ulcers are repaired by the same type of pedicle flaps after excision of the ulcer and projecting bony spines, trochanteric ulcers by amputation of the greater trochanter and a similar closure. Gelb (33) reported on 50 civilian paraplegics with 115 decubiti This group was similar to the veteran cases reported except as to cause and age, being made up of patients from 15 to 62 years of age. The application of previously described principles resulted in a high percentage of successful closures.

Malignant Degeneration

One possible late development in the heavy burn scar or chronic ulceration is the formation of squamous cell carcinoma. This form of malignancy was described by Marjolin in 1828 and today bears his name. The story told by any one of these patients typifies the useless suffering, prolonged disability, and economic loss so commonly associated with the deep ulcer when there is a failure to pursue energetically and intelligently the object of speedy and complete rehabilitation (34). These patients have suffered deep and sizeable areas of injury, and most have been hospitalized for many months with many more months or years elapsing before healing was complete. Healing is allowed to proceed slowly and spontaneously or at best a few pinch grafts are applied. Usually healing is not permanent but repeated breakdown occurs in the fragile epithelium. Often there is marked contracture or other deformity of a part. Over a period of years [in one series the average time was 32.5 years (35)] the constant wound stimulus irritation and infection terminates in malignant changes. Quite often this malignancy is slow to progress. Inasmuch as the cancer is brought about by the inability of a wound to heal because of the dense avascular scar it contains, any form of treatment is wrong except for elimination of the basic condition along with the malignancy. Most of these conditions are best treated by adequate excision and the application of a split thickness skin graft. Some will require resurfacing with a pedicle flap, and those of the extremity which have penetrated deeply will require amputation.

Radiation Injury

Radiation injuries continue to develop even with modern facilities because of the increasing total number of people undergoing radiation exposure. Brown, McDowell & Fryer (36) have described the hazards of the neglected radiation dermatitis as follows:

> The sources are vocational (as in doctors and dentists), therapeutic, diagnostic (as in fluoroscopic examination), commercial epilation, and atomic radiation in laboratory workers or war victims. The injury may result from human error, mechanical error or as a calculated risk as in the treatment of malignancies.
>
> [illegible] from repeated exposures [illegible] [illegible]servative [illegible] sedation, [illegible] as well as grafting of open wounds as soon as it is felt that a free graft or flap will survive. For burns of known surface extent, early excision and repair may be done.
>
> The chronic burn is the type one usually thinks of, such as those seen in the hands of doctors These result most frequently from repeated small exposures over a long period of years, with the lesions always getting worse. Acute burns from single exposures may result in the development of chronic changes also, and for this reason, after subsidence of the acute stage, trouble may still be expected

The lesion in the skin is dangerous because it is a progressive one with

the ultimate result being carcinoma if the patient lives long enough. Wolback (37) reported the pathologic changes in the skin as being coagulation, atrophy, endarteritis of the small arterioles, telangiectasis, clotting of the dilated vessels which gives the "coal spots," epithelial activity to throw the coal spots off which causes keratosis, ulceration, and after a long continued wound stimulus, carcinoma. This course is always progressive and the malignant change may appear at any time after a few years. The most usual type of cancer is squamous cell, but basal cell growths may occur. These malignancies may develop about the periphery of an area of radiation dermatitis in the portion regarded clinically as being less severe.

Since these changes are progressive and irreversible, medical treatment other than protective and soothing applications for palliation does not eliminate the dangerous prognosis. Further radiation whether Beta, Gamma, or sunlight must be avoided. Effective treatment can only be removal of the critically damaged tissue and replacement with free skin grafts or pedicle flaps.

In many instances, excision of the damaged tissue leaves a base suitable for the application of an immediate graft, and this should be the aim where possible. If the progressive character of the lesion is recognized, early skin replacement permits a simple type of repair. Where deeper injury has caused extensive damage, the bed after excision will have such a reduced vitality that a free graft would be expected to fail because of lack of nutrition. Immediate closure by means of a pedicle flap should then be considered. Such a residual wound occasionally will develop a progressive necrosis if left open because its diminished vitality cannot withstand infection

Such a pedicle flap should be of the permanent blood-carrying type rather than a parasitic one in order to bring in an increased blood supply to the avascular area. In radiation lesions of the hands, early excision and grafting is particularly important because the presence of malignancy so often requires amputation of a digit or a larger portion of the hand Frequently the volar surface has not been damaged as much and the graft may be limited to the dorsum. If both dorsum and volar surfaces require resurfacing then each should be done at separate operations.

Repairs of radiation dermatitis are usually permanent. Occasionally there may be late necrosis of underlying structures with resulting ulceration of the overlying graft This late deep necrosis usually follows trauma or infection. The mandible is a typical site, and the process may follow tooth extraction.

FREE SKIN GRAFTS

The type and thickness of a skin graft to be used for a given purpose must be chosen to suit the need. Free skin grafts may be classified as pinch or small deep grafts, full skin thickness or Wolfe grafts, and split skin grafts or grafts of intermediate thickness. The pinch graft is the least efficient and is not often used by plastic surgeons. The full thickness graft has the advan-

tages of a better final appearance, of providing a heavier surface, and of undergoing the least contraction after application. It is less likely to "take" than the thinner split graft and for this reason is not applied except to newly created wounds free from infection where there is a definite need for it. It is not used on granulating wounds. One use is about the face or eyelids to replace excised skin such as in the treatment of malignancies or to relax contractures as in ectropion of the eyelids. Small areas may be grafted using postauricular or supraclavicular skin which grafts readily and best matches the facial skin in color. The palmar surface of the hand and fingers is best surfaced with whole thickness skin where possible to reduce contracture. The powerful flexor muscles of the hand, the normal flexed position of the hand at rest, and the presence of scar tissue pull all tend to further the natural tendency for a palmar graft to undergo contraction with recreation of the original deformity. Thin grafts contract more than thick ones and are therefore ill-advised for this type of coverage.

Split thickness skin grafts serve the greatest variety of need. The graft may be secured in large amounts from most surfaces of the body. It takes readily if held in secure contact with a recipient bed of adequate vascularity, and if not subjected to excessive infection. It will tolerate considerable contamination. Its uses may be extended by varying the thickness of the graft. The thinner the graft the greater the ease of "take," but more contraction may be expected with wrinkling, fibrosis, and reduced surface area Large burns require thin grafts to insure quick healing of both donor sites and burn ulcer, with the possibility of re-using the donor sites for second "crops" of skin.

The donor site of a split thickness skin graft heals by regeneration from the remaining skin appendages. This healing may be very rapid in the case of thin grafts if the donor sites are properly dressed, using fine mesh grease gauze next to the raw surface, covered by a bulky immobilized gauze dressing, and if infection does not intervene. Healing may be slow or absent when grafts are cut too thick, when the donor site is dressed improperly, or when infection occurs causing destruction of the remaining epithelial structures. Thus a skin graft which fails under these circumstances may worsen the patient's situation considerably.

The importance of meticulous attention to detail has been stressed in the preliminary care of the wound and the donor site. This is no less important in the care of the graft. The principles are the establishment of a clean wound containing no avital tissue, and the smooth application of the graft to its bed so as to insure continuous contact with no gross movement. Avoidance of hematoma, maintenance of the graft under tension the equivalent of its normal, and the application of a nonirritating dressing (fine mesh grease gauze) which splints and supports the area by its bulk and springy pressure are also important.

It must be remembered that the graft will assume a circulation rather quickly but will not become tough and normally resistant to injury and

infection for some weeks. Thus, the after care is also important. A graft may "take" and then be destroyed by confined infection before it is first dressed. A potentially infected graft must be dressed early, on the third, fourth, or fifth postoperative day, depending on the problem. Purulent material, impounded secretion, and sloughed tissue are gently and completely removed. A dressing is reapplied conforming to that described under the preparation of a burn for grafting, and subsequent dressings are done at 24 or 48 hr. intervals until the graft is out of danger.

The graft may be applied on top of clean granulation tissue where the size of the wound makes the removal of this tissue impractical. The recipient area is cleaner, however, if the granulations are first removed and the graft applied immediately. This causes a greater loss of blood and increases the possibility of hematoma formation underneath the graft. Heavy scar tissue must be removed to achieve a good permanent result.

Autogenous Tissue Grafts

The behavior of free autogenous human tissue grafts has been studied by Peer & Walker (38) and an appreciation of their report is helpful in understanding the possibilities and limitations of tissue transplantation and the management of grafted tissues. One of the conclusions of this study is

> The cells in septal bone, cartilage, fascia, tendon and surface skin grafts all tend to survive, the tissues retaining their specific structure. Thus cartilage appears as cartilage, septal bone as bone, and fascia as fascia, etc., regardless of whether the recipient site consists of like or unlike tissue. There is no evidence of mass replacement of graft cells by infiltrating elements from host tissues as has been stated in the older literature.
>
> The initial survival of the cells in all free tissue grafts is dependent upon two conditions existing at the site of transfer: 1. The cells must be bathed in an isotonic solution to prevent desiccation, and 2 a fluid exchange must eventually reach the cells to provide them with nourishment and relieve them of accumulated waste products.
>
> Tissue fluid exuding from the host site serves to prevent desiccation of the graft cells during the first few days, but this may not be an important factor in providing nourishment for the centrally located cells which are remote from this surface fluid.
>
> Skin grafts prevented from desiccation and stored for four days at body temperature took satisfactorily when reapplied to the donor animal, indicating that the cells in the free skin grafts can remain viable in the absence of any circulating fluid medium for periods up to four days following transplantation

Peer's studies have suggested that the belief that vascularization of a new graft takes place by the ingrowth of host capillaries to replace the old vascular system is not correct, but that a blood circulation is established in less than four days largely or in part by the direct anastomosis between severed vessels in the host tissue and the old vascular system of the graft. This provides an early circulation to all portions of the grafted tissue, including those cells remote from the host surface. This concept explains why the successful free transplantation of tissue is limited to a critical mass or thickness beyond which success may not be expected.

An effort to replace severed features or fingers has usually been unsuccessful despite apocryphal reports to the contrary. Small portions of severed finger tips, as much as the entire pad of the terminal phalanx cut obliquely, or the tip amputated squarely through the distal third of the nail have been permanently replaced. A moderate sized section of avulsed ear with attached postauricular skin has been successfully replaced. Here the postauricular skin took as a free thin graft and its circulation sufficed to carry the greater bulk of ear tissue.

Utilizing this principle, good use has been made of the transplantation of full thickness ear segments, including all components, in replacing loss of a portion of the ala or tip of the nose. Formerly, these repairs necessitated the use of a pedicle flap or some other multiple stage procedure. The rim of the ear approximates the thickness and character of the ala nasae. A good segment of the ala may be replaced with a similar segment from the ear, providing the critical bulk is not exceeded and that the composite graft is so designed as to have the maximum contact with well vascularized host tissue in proportion with its bulk. A long narrow graft has a better chance of success than a wide one with less percentage of its surface sutured to raw host structure.

The transplantation of skin is seen to include many ramifications, and recent advances in medicine have been shown to have affected trends in plastic surgery quite markedly. This is particularly true in reference to burns, but even so, it becomes more and more obvious, as time goes by, that sound surgical principles and basic physiological concepts are of prime importance in this field of surgery.

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ANNOTATED LIST OF REVIEWS IN MEDICINE

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Most of the reviews listed here appeared between October 1951 and November 1952.

Infectious Diseases

1. "Infectious Diseases," Reiman, H. A., *Arch. Internal Med*, 89, 115–60 (1952), 322 references The significant publications in 1951 are reviewed

2. "Tuberculosis," King, D S, *New Engl. J. Med.*, 247, 718–25 (1952), 77 references. A good review of the field intended for those who are not tuberculosis specialists.

3. "B. C. G Vaccination," Partenheimer, R. C., *New Engl. J. Med*, 245, 496–501 (1951), 27 references. A brief compilation and critical review of the results reported in the literature.

4 "Syphilis," Beerman, H, Ford, W T., Nicholas, L. and Katzenstein, L, *Arch Internal Med.*, 89, 309–52, 464–519 (1952), 429 references A review of the most recent literature

5 "Canicola Fever," Haunz, E. A and Cardy, J D., *Arch. Internal Med*, 89, 978–93 (1952), 75 references The world literature is abstracted.

6 "Toxoplasma and Toxoplasmosis," Weinman, D., *Ann. Rev. Microbiol.*, 6, 281–98 (1952), 116 references

7. "Brucellosis in Animals and Man," Stableforth, A W., *Proc Roy. Soc Med*, 45, 79–86 (1952), 39 references. A brief review of the occurrence of the disease in animals.

8 "Some Biologic and Clinical Problems Related to Intracellular Parasitism in Brucellosis," Spink, W W., *New Engl. J. Med*, 247, 603–10 (1952), 65 references. An interesting discussion of the host-parasite relationship in Brucellosis.

9. "Symposium on the Biology of Bacterial Spores," Williams, O B., *et al.*, *Bact Revs.*, 16, 89–143 (1952), 109 references An intense review of the field under ten different subject headings

10. "Bacterial Transformation Reactions," Austrian, R, *Bacteriol. Revs*, 16, 31–50 (1952), 43 references A highly technical nonclinical summary.

11. "The Human Rickettsioses," Bell, E J., and Philip, C. B, *Ann Rev. Microbiol.*, 6, 91–118 (1952), 185 references.

12 "Classification and Nomenclature of Viruses," Andrewes, C. H., *Ann. Rev Microbiol.*, 6, 119–38 (1952), 72 references

13. "The Coxsackie Viruses and Human Disease," Kilbourne, E. D., *Am J. Med Sci*, 224, 93–102 (1952), 59 references. A brief summary of the literature

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14. "The Importance of Coxsackie Viruses in Human Disease, Particularly Herpangina and Epidemic Pleurodynia," Huebner, R. J., Beerman, E. A., Cole, R. M., Beigelman, P. M., and Bell, J. A., *New Engl. J. Med*, 247, 249–56, 285–89 (1952), 91 references. An excellent and timely review of a subject having much current interest.

15. "Aspects of the Influenza Problem," Mulder, J., *Advances Internal Med.*, 5, 337–71 (1952), 86 references. A fine review for the clinician.

16. "Haemagglutination in Relation to Host Cell-Virus Interaction," Burnet, F. M, *Ann. Rev. Microbiol.*, 6, 229–46 (1952), 110 references.

17. "Significance of Antigenic Variation of Influenza Viruses in Relation to Vaccination in Man," Francis, T., Jr., *Federation Proc.*, 11, 808–12 (1952) 18 references.

18. "A Pattern of Antigen Variations," Hilleman, M. R., *Federation Proc.*, 11, 798–803 (1952), 37 references. Deals with the variation in influenza viruses and their use in vaccination.

19. "Biological Selection of Antigenic Variants," Horsfall, F. L., Jr, *Federation Proc.*, 11, 804–7 (1952), 32 references. Concerned with influenza virus.

20. "Poliomyelitis," Boyer, R, and Greenspan, W, *Arch. Pediat.*, 69, 296–309, 334–54 (1952), 135 references. An all-inclusive review.

21. "Present Concepts and Recent Advances in Acute Poliomyelitis," Paul, J. R, *Arch. Internal Med.*, 90, 271–79 (1952), 38 references. New knowledge and changes in point of view are summarized.

22 "A Comparison of the Clinical Features of Poliomyelitis in Adults and in Children," Weinstein, L., Shelokov, A., Seltser, R., and Winchell, G D., *New Engl. J. Med.*, 246, 296–302 (1952), 8 references. Chiefly a review of personal experiences.

23. "Tracheotomy in Bulbar Poliomyelitis; a Review," Neffson, A. H., *Am. J. Med. Sci.*, 224, 465–81 (1952), 45 references A critical survey of the literature.

24. "Immunity to Poliomyelitis," Gear, J., *Ann Internal Med.*, 37, 1–22 (1952), 42 references A brief review of some of the public health aspects of the disease

25 "Tick Paralysis on the Atlantic Seaboard," Costa, J. A, *Am J. Diseases Children*, 83, 336–47 (1952), 43 references A review of published cases and their incidence during the poliomyelitis season

Public Health

1. "Epidemiological Methods in Preventive Medicine," Cruickshank, R., *Proc. Roy. Soc. Med.*, 45, 621–8 (1952), 18 references Evidence that application of the epidemiological method will lead to advances in medicine comparable to clinical and laboratory methods.

2. "Animal Diseases of Public Health Significance," Steele, J. H., *Ann. Internal Med.*, 36, 511–24 (1952), 65 references. A very brief well-considered summary.

3. "Occupational Medicine," Hardy, H. L., *New Engl. J. Med.*, 247, 473–83, 515–24 (1952), 248 references. A fine analysis of the recent pertinent literature.

4. "Background to Britain's Health Service," Clegg, H., *New Engl. J. Med*, 247, 435–39 (1952). An interesting and apparently unbiased summary of a much debated project.

5. "Factors to be Considered in Planning a Health Center," Wallace, H. M., Losty, M. A., and Baumgartner, L., *Am. J. Diseases Children*, 83, 54–64 (1952), 13 references. Has special reference to a large city.

6 "Industrial Noise: Its Medical, Economic and Social Aspects," Fox, M. S., *Am. J. Med. Sci.*, 223, 447–60 (1952), 54 references A critical review of the current status of the subject.

DISEASES OF THE GASTROINTESTINAL TRACT

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4. "Motility of the Alimentary Canal in Man," Code, C. F., Hightower, N C., and Morlock, C. G., *Am J. Med.*, 13, 328–51 (1952), 113 references A review of recent studies.

5. "Neural Regulation of Gastric and Intestinal Motility," Youmans, W. B., *Am. J. Med.*, 13, 209–26 (1952), 142 references. An excellent summary of the subject.

6 "A Physiologic and Clinical Consideration of the Pressures Developed in the Digestive Tract," Quigley, J P. and Brody, D. A., *Am. J. Med.*, 13, 73–81 (1952), 17 references. Various techniques and methods are analyzed.

7. "Use of Antibiotics in Gastrointestinal Diseases," Kirsner, J. B., Levin, E., and Palmer, W. L., *Arch Internal Med.*, 90, 677–706 (1952), 440 references. A herculean task of literature summarization covering the years since these agents were introduced.

8. "A Review of the Literature on Preoperative Prophylaxis of the Bowel with Antibacterial Agents," Riddell, M. I, *Am. J. Med Sci*, 223, 301–15 (1952), 97 references

9. "Familial Intestinal Polyposis," Dukes, C. E., *Ann Roy Coll. Surg.*, 10, 293–304 (1952), 3 references. An interesting summary of an hereditary disease.

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12. "Volvulus of the Stomach," Dalgaard, J. B., *Acta Chir. Scand.*, 103, 131–53 (1952), 131 references. A complete but concise survey of the literature accompanying a case report.

13. "Massive Bleeding from the Upper Gastrointestinal Tract," Jacobson, L. F., and Johnston, C. G., *Am. J. Med. Sci.*, 224, 219–28 (1952), 77 references. Current views are emphasized.

14. "Cholecystitis in Childhood; Associated Obstructive Jaundice," Ulin, A. W., Nosal, J. L., and Martin, W. L., *Surgery*, 31, 312–26 (1952), 68 references. The literature on the subject is brought up to date, well summarized and critically reviewed.

15. "Routine Cholangiography at Operations for Gall Stones," Swedberg, J., *Acta Chir. Scand.*, 103, 175–93 (1952), 28 references. A review of Swedish experience covering 700 cases.

16. "Agenesis of the Vermiform Appendix," Collins, D. C., *Am. J. Surg.*, 82, 689–96 (1952), 87 references. A review of the literature which covers 57 cases.

17. "The Recent Advances in the Management of Pancreatitis, Acute and Chronic," Hinton, J. W., *Bull. N. Y. Acad. Med.*, 28, 425–39 (1952), 49 references. A short summary of current concepts and practice.

18 "Progress Report on Acute Intestinal Obstruction," Nemir, P., Jr., *Am. J. Med. Sci.*, 223, 198–204 (1952), 102 references. A reviewof the reports of the past 11 years.

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20. "The Surgical Treatment of Cirrhosis of the Liver," Stock, F. E., *Ann. Roy. Coll. Surg.*, 10, 187–207 (1952), 19 references. A short clinical résumé.

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4. "Factors Determining the Contour of Pressure Pulses Recorded from the Aorta," Alexander, R. S , *Federation Proc.*, **11**, 738–49 (1952), 20 references.

5. "Volume Quantitation of the Aortic Pressure Pulse," Remington, J. W., *Federation Proc.*, **11**, 750–61 (1952), 12 references.

6. "Certain Physical Characteristics of the Cardiovascular System and Their Significance in the Problem of Calculating Stroke Volume from the Arterial Pulse," Peterson, L H., *Federation Proc.*, **11**, 762–66 (1952), 4 references

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8 "Structure and Physiological Functions of Ferritin," Granick, S., *Physiol. Revs*, **31**, 489–511 (1951), 46 references. A review of the recent revival of interest in the possible relation of this iron metabolism compound to homeostasis of the circulation.

9. "On Consistency in Convention of Sign in Electro-cardiography and Vectocardiography," Robertson, D., *Am. Heart J.*, **42**, 912–44 (1951), 46 references. Strictly for the cardiologist.

10. "The Electrocardiogram and the Position of the Heart," Johnston, F. D., Ryan, J. M., and Bryant, J. M , *Am Heart J.*, **43**, 306–15 (1952), 20 references A short, highly specialized review.

11. "The Electrocardiographic Exercise Test," Scherf, D., and Schaffer, A I., *Am Heart J.*, **43**, 927–46 (1952), 85 references. For the cardiologist and clinical physiologist.

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16 "Catheterization of the Heart," Bing, R. J , *Advances Internal Med.*, **5**, 59–141 (1952), 200 references. A review of the data on cardiac output and intracardiac pressures obtained with this method.

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18. "Traumatic Heart Disease," Kissane, R. W., *Circulation*, **6**, 421–25 (1952), 11 references. A very brief survey of the literature on nonpenetrating injuries.

19. "Intracranial Thrombophlebitis," Symonds, C., *Ann. Roy. Coll. Surg.* 10, 347–56 (1952), 8 references. A clinical summary.

20. "Humoral and Vasomotor Control of Bloodvessels," Page, I. H., *Bull. N. Y. Acad. Med.*, 28, 131–44 (1952), 32 references. These factors are reviewed in the light of their possible relation to hypertension.

21. "Portal Hypertension and Its Treatment," Blakemore, A. H., *Advances Internal Med.*, 5, 142–64 (1952), 37 references. A complete survey and discussion of the subject.

22. "Hypertension and the Problem of Vascular Homeostasis," Page, I. H., and Corcoran, A. C., *Circulation*, 6, 286–92 (1952), 18 references. Poses many questions on the basis of our present knowledge.

23. "Hypertension in Children: A Review," McCrory, W. W., *Am. J. Med. Sci*, 223, 671–80 (1952), 106 references.

24. "The Pathogenesis of Malignant Hypertension," Pickering, G W., *Circulation*, 6, 599–612 (1952), 67 references. A critical review of the subject.

25. "Sympathectomy for Essential Hypertension," Allen, E. V., *Circulation*, 6, 131–40 (1952). A personal review of the author's experience and opinions.

26. "Coronary Disease: Clinical-Pathologic Correlations and Physiology," Blumgart, H. L., *Bull. N. Y. Acad. Med.*, 27, 693–710 (1951), 16 references.

27. "The Clinical Recognition of Coronary Heart Disease," Levy, R. L., *Bull. N. Y. Acad. Med.*, 27, 711–22 (1951), 19 references.

28 "The Functional Importance of Coronary Collaterals," Wiggers, C. J., *Circulation*, 5, 609–15 (1952), 17 references. A comparison of all types of experimental data.

29. "Electrolytes and Congestive Failure," Danowski, T. S., *Ann. In-* [illegible] history of the

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31. "Edema and Dyspnea of Heart Failure," Stead, E. A., Jr, *Bull. N. Y. Acad. Med.*, 28, 159–67 (1952). 10 references. A brief provocative discussion.

32. "The Mechanism and Management of Circulatory Failure," Dock, W., *Bull. N. Y. Acad. Med*, 27, 645–52 (1951), 8 references. A unique presentation.

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34. "Cardiac Asthma," Lombardo, T. A., and Harrison, R. T., *Circulation*, 4, 920–29 (1951), 32 references A summary of recent clinical progress.

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38. "Surgery of Acquired Valvular Disease," Wylie, R W., *Bull. N. Y. Acad. Med*, 28, 106–17 (1952), 22 references.

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40 "Studies in Mitral Stenosis," Ellis, L. B, *et al.*, *Arch Internal Med*, 88, 515–31, 532–47 (1951), 89, 970–77 (1952), 60 references An extensive review of personal experiences

41. "The Surgical Treatment of Patent Ductus Arteriosus," Ekstrom, G., *Acta Chir. Scand. Suppl*, 169, 1–197 (1952), 461 references

42. "Surgery of the Heart and Great Vessels," Sweet, R H, and Scannell, J. G., *New Engl. J. Med.*, 247, 18–24, 56–60 (1952), 82 references. A review of the present status of cardiac surgery with emphasis on procedures of established value.

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20. "Humoral and Vasomotor Control of Bloodvessels," Page, I. H., *Bull. N. Y. Acad. Med.*, 28, 131–44 (1952), 32 references. These factors are reviewed in the light of their possible relation to hypertension.

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5. "Lids, Lacrimal Apparatus, and conjunctiva," Allen, J. H., *Arch. Ophthalmol*, 47, 87–112 (1952), 226 references. A review of the recent literature

6. "Diseases of the Uveal Tract," Hogan, M. J., *Arch. Ophthalmol.*, 47, 383–409 (1952), 203 references. The literature of 1950–51 is covered.

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3. "The Gram Stain," Bartholomew, J. W., and Mittwer, T., *Bacteriol. Rev.*, 16, 1–29 (1952), 150 references. For the bacteriological specialist.

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